بسم الله الرحمن الرحيم

تتقدم **لجنة الطب والجراحة** لكم بهذه الدوسية الخاصة **بمادة الأطفال** / جامعة مؤتة ..

و التي تحتوي على مادة **السنة السادسة كاملة** ، والتي ساهم بإعدادها الطالبة :

مارلين معن حجازين

وأشرف على طباعتها وتنسيقها الطالب :

طارق نظمي أبولبدة

نسأل الله أن يكتب فيها النفع والفائدة ، ونرجو منكم تقديم التغذية الراجعة بملاحظاتكم الرامية لتحسين جودة هذه الدوسية ..

" يَا غُلَامُ إِنِّي أُعَلِّمُكَ كَلِمَاتٍ :

احْفَظْ اللَّهَ يَحْفَظْكَ ؛ احْفَظْ اللَّهَ تَجِدْهُ تُجَاهَكَ ..

إِذَا سَأَلْتَ فَاسْأَلْ اللَّهَ ، وَإِذَا اسْتَعَنْتَ فَاسْتَعِنْ بِاللَّهِ ..

وَاعْلَمْ أَنَّ الْأُمَّةَ لَوْ اجْتَمَعَتْ عَلَى أَنْ يَنْفَعُوكَ بِشَيْءٍ لَمْ يَنْفَعُوكَ إِلَّا بِشَيْءٍ قَدْ كَتَبَهُ اللَّهُ لَكَ ..

وَلَوْ اجْتَمَعُوا عَلَى أَنْ يَضُرُّوكَ بِشَيْءٍ لَمْ يَضُرُّوكَ إِلَّا بِشَيْءٍ قَدْ كَتَبَهُ اللَّهُ عَلَيْكَ ..

رُفِعَتْ الْأَقْلَامُ وَجَفَّتْ الصُّحُفُ "

فهرس المواضيع

Acid base balance

- **Normal serum electrolyte and arterial blood gas values (ABG values)**

  - **pH** 7.35-7.45
  - **HCO3-** 22-26mmol/L (Av. 24 mmol/L)
  - **Cl-** 96-106 mmol/L
  - **K+** 3.5-5 mmol/L
  - **Na+** 135-145 mmol/L
  - **pO2** 80-100mmHg
  - **pCO2** 35-45 mmHg (Av.40 mmHg)

- **Mechanism of regulation of pH**

  - **First line of defence:** Buffers (instantaneous)
  - **Second line of defence:** Respiratory regulation (6-24hr)
  - **Third line of defence:** Renal regulation (24h-5days)
  - **Renal regulation is supplemented by: Liver**

- **Bicarbonate Buffer System**

Most important buffer of ECF.

- **CO2+H2O------H2CO3….H+ +HCO3-**

Phosphate Buffer

- Mainly intracellular, effective at a wide pH range
- Most important buffer in the urine (K_2HPO_4 / KH_2PO_4)
- Even in mild acidosis, bone phosphate is released into plasma to maintain the ratio
- In chronic acidosis, bone could be decalcified
- **OH- +H2PO4-….H2O +HPO4-2 ALKALOSIS**
  H+ +HPO4-2 ….H2PO4- ACIDOSIS

Protein Buffers

- Buffering capacity depends on the amino acids in the protein (ionizable side-chains)

- **Role of Lungs in acid base balance**

- The lungs prevent an increase in the Pco2 in the blood by excreting the CO2 that the body produces the rapid pulmonary response (usually within 6 to 24 hours) to changes in the CO2 concentration occurs via central sensing of the Pco2 and a subsequent increase or decrease in ventilation to maintain a normal Pco2 (35-45 mm Hg).
- An increase in ventilation decreases the Pco2, and a decrease in ventilation increases the Pco2

- **role of kidney in acid base balance**

- **Kidney regulates acid base homeostasis by 3 mechanisms:**

1. Proton secretion

2. Bicarbonate reabsorption
3. Bicarbonate generation

- **Acidosis** → H^+ secreted → acidic urine
- **Alkalosis** → HCO_3^- excreted → alkaline urine

- **Secretion of protons**

- Protons from fixed acids are constantly secreted by proximal tubular cells, distal tubular cells and collecting duct cells in to the lumen
- Predominantly Na^+- dependent in proximal tubules
- Relatively Na^+- independent in distal tubules and collecting ducts, either ATP driven proton pump or H^+-K^+ ATPase

- **Bicarbonate reabsorbtion**

Occurs mainly in proximal tubules

- Na^+-K^+ ATPase on basolateral membrane moves Na^+ from tubular cell to interstitium
- The low intracellular Na^+ drives the entry of Na^+ from tubular lumen to cell, helps in easy secretion of H^+
- No net gain of bicarbonate
- No net loss of hydrogen ions
- **<u>Maintains steady state but cannot correct an acidosis</u>**

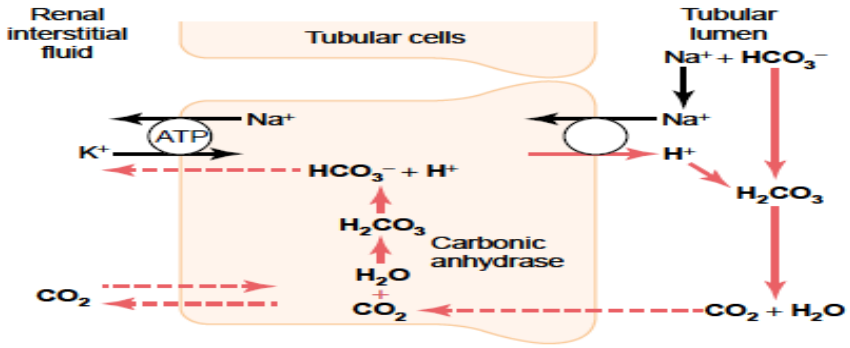


Figure 30–5

Cellular mechanisms for (1) active secretion of hydrogen ions into the renal tubule; (2) tubular reabsorption of bicarbonate ions by combination with hydrogen ions to form carbonic acid, which dissociates to form carbon dioxide and water; and (3) sodium ion reabsorption in exchange for hydrogen ions secreted. This pattern of hydrogen ion secretion occurs in the proximal tubule, the thick ascending segment of the loop of Henle, and the early distal tubule.

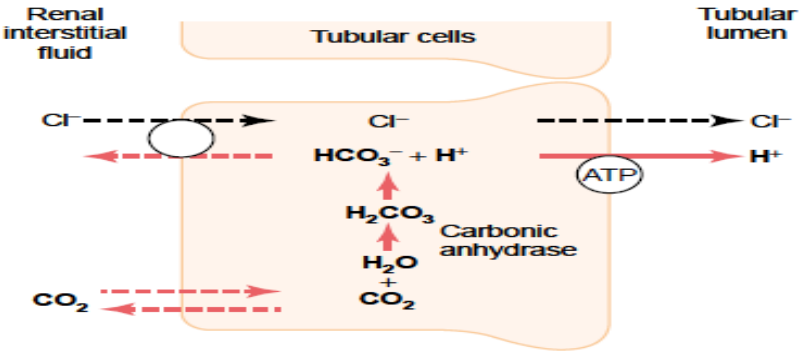
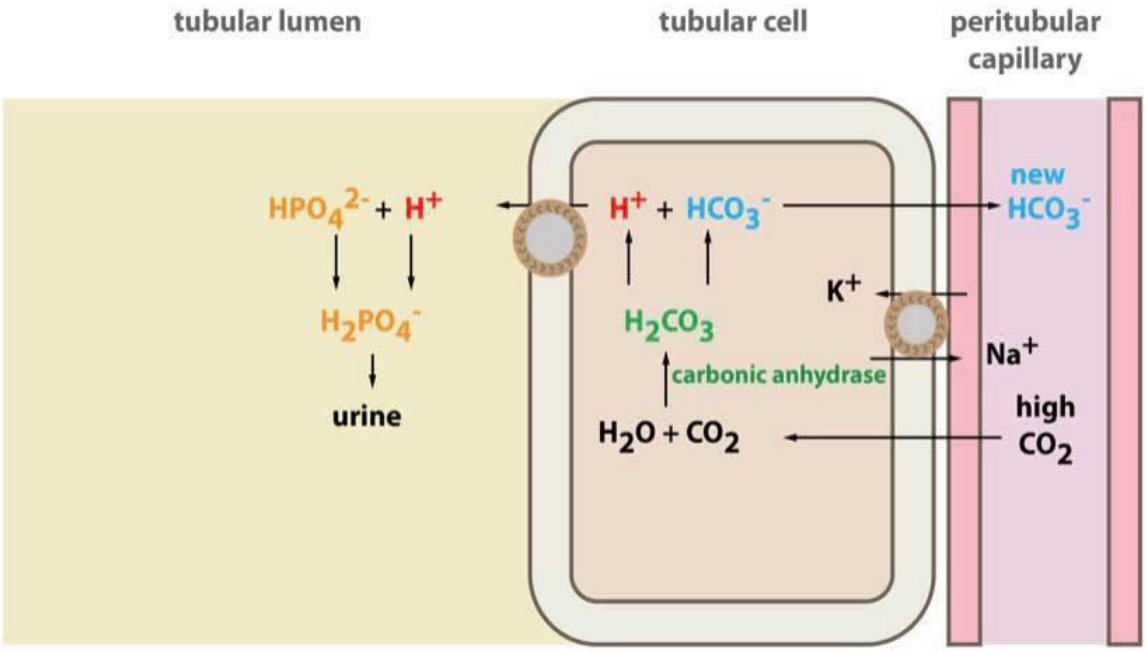


Figure 30–6

Primary active secretion of hydrogen ions through the luminal membrane of the intercalated epithelial cells of the late distal and collecting tubules. Note that one bicarbonate ion is absorbed for each hydrogen ion secreted, and a chloride ion is passively secreted along with the hydrogen ion.

- **Bicarbonate generation**

- Production of new bicarbonate to add to alkali reserve
- Net loss of protons from the body
- Net gain of bicarbonate
- Can correct an acidosis
- Depends on the presence of other buffer bases Eg. Phosphate, ammonia
- Phosphate buffer functions mainly in distal tubules and collecting ducts
- Ammonia buffer functions mainly in proximal tubules and collecting ducts



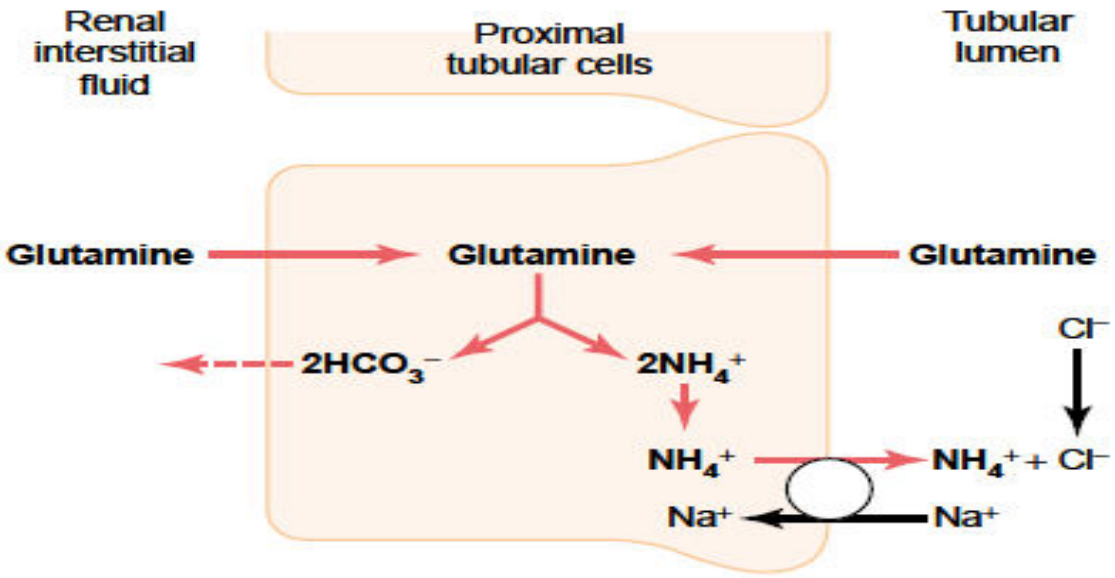


Figure 30–8

Production and secretion of ammonium ion (NH_4^+) by proximal tubular cells. Glutamine is metabolized in the cell, yielding NH_4^+ and bicarbonate. The NH_4^+ is secreted into the lumen by a sodium-NH_4^+ pump. For each glutamine molecule metabolized, two NH_4^+ are produced and secreted and two HCO_3^- are returned to the blood.

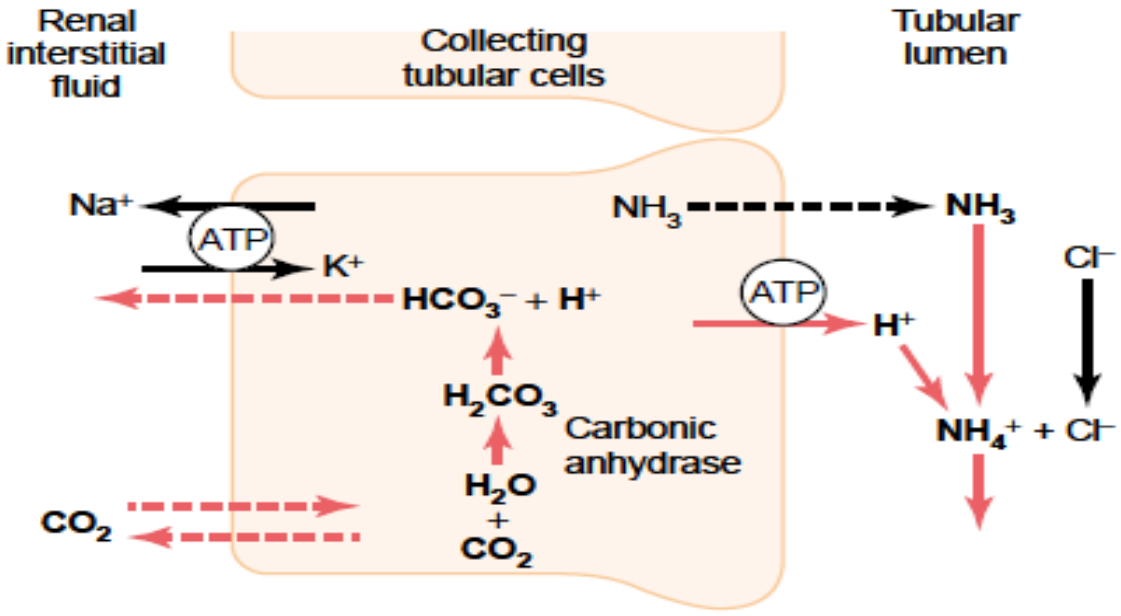


Figure 30–9

Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules. Ammonia diffuses into the tubular lumen, where it reacts with secreted hydrogen ions to form NH_4^+, which is then excreted. For each NH_4^+ excreted, a new HCO_3^- is formed in the tubular cells and returned to the blood.

- **Role of ammonia buffer in bicarbonate generation**
- Functions when all other buffers have been depleted
- Very important in severe or chronic acidosis

Acidosis :

- **Acidemia**: Decrease in blood pH (below 7.38)
- **Acidosis**: Any process that can lead to acidemia.
- Acidosis can be respiratory (due to change in pCO2) or metabolic (due to change in [HCO3-])

Compensatory response :

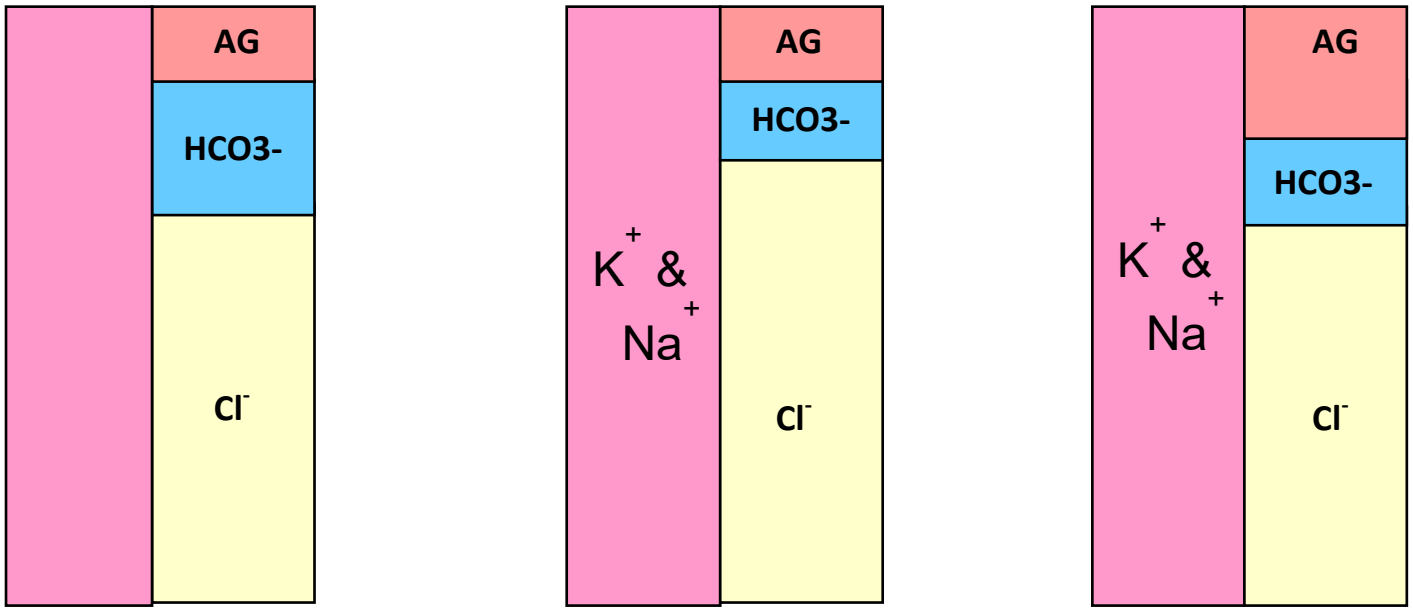
- Body tries to correct the disorder by an adaptive response
- Adaptive (compensatory) response is in the direction of the primary disturbance (in simple disturbances)
- Compensatory response tries to restore the pH to normal

Anion Gap :

- Normally, [cations] = [anions] for electrical neutrality
- Plasma cations measured in lab are Na+ & K+ (contributes to 95% of total cations)
- Plasma anions measured in the lab are HCO3- & Cl- (contributes to 80% of total anions)
- Anion gap = difference between the conc.of measured cations and measured anions
- Represents the unmeasured anions in plasma
- Unmeasured anions include protein , phosphate, sulfate, urate & organic acids
- $A = (Na^+ + K^+) - (HCO_3^- + Cl^-)$
- **Normal anion gap is 12-14 mEq/L**

Metabolic acidosis

Normal **hyperchloremic** **High Anion Gap**



- **Metabolic acidosis**

- Primary change: ↓ [HCO_3^-]
- Compensatory change: Hyperventilation (to↓pCO_2)
- Causes:

- **Normal anion gap (hyperchloremic)**	- **High anion gap (normochloremic)**
- Renal tubular acidosis	- Ketoacidosis
- Diarrhea	- Lactic acidosis
- Carbonic anhydrase inhibitors	- Renal failure
- Hypoaldosteronism	- Toxins

- **pH and plasma potassium**

- During acidemia, there may be exchange of H^+ in blood with K^+ in ICF to maintain pH of blood
- Therefore, acute acidosis → hyperkalemia
  acute alkalosis → hypokalemia
- When you try to correct acidosis, K^+ may suddenly go back to cells→ hypokalemia
- Hence, important to maintain potassium balance during correction of acidosis

☒ **Ex :**

Na+ = 138
HCO3- = 14
Cl- = 108
K+ = 4
Anion Gap = (138+4) – (108+14)
= 20 → wide anion Gap

- Hypoalbuminemia can mask an increased concentration of gap ions and lowering the value of AG
- Adjusted AG = AG +2.5 x (normal albumin – actual albumin)

Example: Pt. albumin 2.0g/dL and AG 15

15 + 2.5 x (4 – 2) = 15 + 5
Adjusted AG = 20

Metabolic Acidosis

- **Etiology and Pathophysiology**

- Loss of bicarbonate from the body
- Impaired ability to excrete acid by the kidney
- Addition of acid to the body (exogenous or endogenous)

- **Loss of bicarbonate from the body :**

- Mainly by GI loses; diarrhea or vomiting. Diarrhea, the most common cause of metabolic acidosis in children, causes a loss of bicarbonate from the body
- Impaired ability to excrete acid by the kidney:
- This condition seen in kidney failure.

- **Addition of acid to the body (exogenous or endogenous):**

- **Lactic acid**: occur by:
  - Incomplete oxidation of carbohydrates (glucose) – this is the main way -, which will convert the glucose into lactic acid. In child with normal liver, the liver can convert it into co2 but in liver failure the lactic acid going to accumulate in the body causing what is called lactic acidosis. The lactic acid production can be increased by; hypoxia, anemia or in shock state.
  - Short bowel syndrome resulting from small bowel resection can have bacterial overgrowth. In these patients, excessive bacterial metabolism of glucose into d-lactic acid can cause a lactic acidosis.
  - Inborn errors of metabolism
  - Drugs: for example propofol and metformin especially in renal failure patients.

- **Ketoacidosis:**

- Incomplete oxidation of triglycerides is the main cause for it.
- This condition can be seen in:
  - Insulin dependent DM
  - Starvation ketoacidosis
  - Alcoholic ketoacidosis which is rare in children

- **Poisoning**: for example salicylates.

- **Clinical Manifestations**

- The clinical manifestations are related to the degree of acidemia!
- The underlying disorder usually produces most of signs and symptoms with mild to moderate metabolic acidosis.
- Compensation and less severe acidemia.. have fewer manifestations
- At a serum pH less than 7.20, there is impaired cardiac contractility and an increased risk of arrhythmias, especially if underlying heart disease or other predisposing electrolyte disorders are present.
- With acidemia there'll be a decrease in the CV response to catecholamine, potentially exacerbating hypotension in children with volume depletion or shock.
- Acidemia causes vasoconstriction of the pulmonary vasculature.
- Chronic metabolic acidosis causes failure to thrive and bone resorption.
- Respiratory compensation(Hyperventilation) in patients with metabolic acidosis:
  - The body compensates for metabolic acidosis by creating hyperventilation which creates respiratory alkalosis.

- This mechanism may work with mild metabolic acidosis but can cause increased respiratory effort with worsening acidosis

The acute metabolic effects of acidemia include:

- Insulin resistance
- Increased protein degradation
- Reduced ATP synthesis

- The acidemia causes the potassium to shift from intracellular to extracellular space thereby there will be Hyperkalemia.
- Severe acidemia will impair brain metabolism and eventually may result in lethargy and coma.

Diagnosis

- ABGs & electrolytes
- Calculate anion gap (AG).
- Serum glucose
- KFT (Cr&BUN), Urinalysis , calculate Urine anion Gap
- Tox. Screen

Interpreting ABGs

- PH
- HCO3 , CO2
- Compensation
- Anion GAP

The One & a Half plus 8 Rule - for Metabolic Acidosis

Expected pCO2 = 1.5 x [HCO3] + 8 (range: +/- 2)

Comments:

- Maximal compensation may take 12-24 hours to reach
- The limit of compensation is a pCO2 of about 10 mmHg

Example: A patient with a metabolic acidosis ([HCO3] 14mmol/l) has an actual pCO2 of 30mmHg.

The expected pCO2 is (1.5 x 14 + 8) which is 29mmHg.

Matches the actual value of 30 so compensation is maximal , no evidence of respiratory acid-base disorder

If the actual pCO2 was 45mmHg and the expected was 29mmHg, then ????

- **ABG: 7.22 / 30 / 10**
- Na 139, K 4.0, Cl 90, C02 10

(1.5 x 10) + 8 = 23

23 ± 2 is < measured PaC02 (30)

Expected PC02 = 23

Conclusion – Not completely compensated

PH :7.22
HCO3 :10
pCO2 :30

- **Delta Ratio**

  For wide anion Gap metabolic acidosis

  . ▲ AG - ▲HCO3 → (-5 , 0 , +5)

  . (AG-12)-(24-HCO3)

  . -5 → normal wide metabolic acidosis

  . +5 →mixed metabolic acidosis+ alkalosis

  . 0 → pure wide anion gap metabolic acidosis

- **Urine anion gap**
  - May be helpful in the evaluation of patients with non-AG metabolic acidosis; to differentiate RTA from other causes(GI).

    UAG = NA + K – CL

  - **Positive** UAG means **Renal** cause.
  - **Negative** UAG means **GI** and other causes.

- **Differential Diagnosis of Metabolic Acidosis with Increased AG**
  - **M**: Methanol
  - **U**: Uremia
  - **D**: DKA or Alcoholic ketoacidosis, Drugs.
  - **P**: Paraldehyde
  - **I** : Ischemia , Isoniazid or Iron toxicity
  - **L** : Lactate [Lactic acidosis]
  - **E** : Ethylene glycol (antifreeze)
  - **S** : Starvation or Salicylates.

  - **Metabolic acidosis:**

  1- Ketosis:
  . DKA
  . Starvation
  . Alcohol ketoacidosis

  2- Poisoning:
  . Ethylene glycol (Antifreeze)
  . Paraldehyde
  . Methanol

- **Differential Diagnosis of metabolic acidosis with normal AGD : Diarrhea**
  - **U** : Ureteral diversion
  - **R** : Renal tubular acidosis
  - **H** : Hyperalimentation: Administration or consumption of nutrients beyond minimum normal requirements, in an attempt to replace nutritional deficiencies.
  - **A** : Acetazolamide or Ammonium chloride
  - **M** : Miscellaneous (amphotericin B, toluene*, others)

- **Treatment**
  - The most effective therapeutic approach is to treat the underlying cause.
  - Insulin in diabetic ketoacidosis or restoration of adequate perfusion in lactic acidosis .
  - In salicylate poisoning, alkali administration .
  - Short-term base therapy is often necessary in other poisonings and inborn errors of metabolism.
  - The use of bicarbonate therapy; examples include RTA and chronic renal failure.

- **Complications of bicarbonate infusion ?**
  - Hypokalemia (most important .. Cardiac arrhythmias)
  - Hypocalcemia (Potassium and calcium should be normal before starting bicarbonate therapy)
  - Hemodialysis is an appropriate choice in Pt with renal insufficiency especially if significant uremia or Hyperkalemia is also present.

CASE REPORT

- **A 7 year-old girl presents with fever and profuse diarrhea for 2 days : vital signs (temp 38.5, HR 130, BP 78/30)**

  PH 7.29 **Na 128**
  PaCo2 30 **Cl 94**
  HCO3 14

  - Step 1: check PH → Acidemia
  - Step 2: check CO2 → Metabolic acidosis
  - Step 3: evaluate compensation → PaCo2=1.5(Hco3)+8
    =29 (compensated)
  - Step 4:calculate anion gap →AG=Na-(Cl+HCO3)
    =20 mEq/L (elevated gap)
  - Step 5:If AG is elevated calculate Delta ratio →=(AG-12)-(24-Hco3)
    =(20-12)-(24-14)
    = -2

  Elevated gap metabolic acidosis +Normal gap metabolic acidosis

- **A 5 year-old boy presents with fever nausea , vomiting and abdominal pain for 1 day**

  PH 7.27 **Na 140**
  PaCo2 27 **Cl 98**
  HCO3 12

  - Step 1: check PH → Acidemia
  - Step 2: check CO2 → Metabolic acidosis
  - Step 3: evaluate compensation → PaCo2=1.5(Hco3)+8
    =26 (compensated)
  - Step 4:calculate anion gap →AG=Na-(Cl+HCO3)
    =30 mEq/L (elevated gap)
  - Step 5:If AG is elevated calculate Delta ratio →=(AG-12)-(24-Hco3)
    =(30-12)-(24-12)
    = +6

  Elevated gap metabolic acidosis +metabolic alkalosis.

Hypertension in children

high BP, including HTN, is defined from normative distribution of BP data in healthy children. This is in contrast to adult HTN, which is primarily defined by clinical outcome data (ie, risk of cardiovascular disease [CVD] and mortality) from large trials of antihypertensive therapy. However, these outcome measures cannot be applied to children because cardiovascular (CV) events other than left ventricular hypertrophy do not typically occur in childhood

- So , **Hypertension** is defined as average SBP and/or diastolic BP (DBP) that **is ≥ 95th** percentile for **gender, age, and height** on **at least 3 occasions.**
- In children, definitions that categorize BP values were modified by the 2017 AAP guidelines into **two age groups** . Of note, **the newly revised definitions for adolescents are aligned with adult guidelines for the detection of chronic elevated BP**. With an acute elevation of BP, it is the magnitude and the rate of increase above baseline that determines the risk of serious morbidity and, at times, mortality.

2017 American Academy of Pediatrics updated definitions for pediatric blood pressure categories

	For children aged 1 to 13 years	For children aged ≥13 years
Normal BP	Systolic and diastolic BP <90th percentile	Systolic BP <120 and diastolic BP <80 mmHg
Elevated BP	Systolic and diastolic BP ≥90th percentile to <95th percentile, or 120/80 mmHg to <95th percentile (whichever is lower)	Systolic BP 120 to 129 and diastolic BP <80 mmHg
Stage 1 HTN	Systolic and diastolic BP ≥95th percentile to <95th percentile+12 mmHg, or 130/80 to 139/89 mmHg (whichever is lower)	130/80 to 139/89 mmHg
Stage 2 HTN	Systolic and diastolic BP ≥95th percentile+12 mmHg, or ≥140/90 mmHg (whichever is lower)	≥140/90 mmHg

BP: blood pressure; HTN: hypertension.

- the diagnosis of persistent childhood HTN is made when repeat blood pressure (BP) values on **three** separate visits are **greater than the 95th percentile for the age, gender, and height of the patient, or it is ≥130/80 mmHg** .

- Because height and gender are important determinants of pediatric BP, BP levels are interpreted based on gender, age, and height :

Blood pressure levels for boys by age and height percentile

BP (percentile)	Systolic BP (mmHg)							Diastolic BP (mmHg)						
	Height percentile or measured height							Height percentile or measured height						
	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1 year														
Height (in)	30.4	30.8	31.6	32.4	33.3	34.1	34.6	30.4	30.8	31.6	32.4	33.3	34.1	34.6
Height (cm)	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
50th	85	85	86	86	87	88	88	40	40	40	41	41	42	42
90th	98	99	99	100	100	101	101	52	52	53	53	54	54	54
95th	102	102	103	103	104	105	105	54	54	55	55	56	57	57
95th + 12 mmHg	114	114	115	115	116	117	117	66	66	67	67	68	69	69

Example : 5 yr old girl that measured 115 cm …. What's the normal BP for her ?

Blood pressure levels for girls by age and height percentile

BP (percentile)	Systolic BP (mmHg)							Diastolic BP (mmHg)						
	Height percentile or measured height							Height percentile or measured height						
	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
5 years														
Height (in)	40.8	41.5	42.6	43.9	45.2	46.5	47.3	40.8	41.5	42.6	43.9	45.2	46.5	47.3
Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120.0	103.6	105.3	108.2	111.5	114.9	118.1	120.0
50th	90	91	92	93	94	95	96	52	52	53	55	56	57	57
90th	104	105	106	107	108	109	110	64	65	66	67	68	69	70
95th	108	109	109	110	111	112	113	68	69	70	71	72	73	73
95th + 12 mmHg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
2 years														
Height (in)	33.9	34.4	35.3	36.3	37.3	38.2	38.8	33.9	34.4	35.3	36.3	37.3	38.2	38.8
Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
50th	87	87	88	89	89	90	91	43	43	44	44	45	46	46
90th	100	100	101	102	103	103	104	55	55	56	56	57	58	58
95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
95th + 12 mmHg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3 years														
Height (in)	36.4	37.0	37.9	39.0	40.1	41.1	41.7	36.4	37.0	37.9	39.0	40.1	41.1	41.7
Height (cm)	92.5	93.9	96.3	99.0	101.8	104.3	105.8	92.5	93.9	96.3	99.0	101.8	104.3	105.8
50th	88	89	89	90	91	92	92	45	46	46	47	48	49	49
90th	101	102	102	103	104	105	105	58	58	59	59	60	61	61
95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
95th + 12 mmHg	118	118	119	119	120	121	121	72	73	73	74	75	76	76

4 years														
Height (in)	38.8	39.4	40.5	41.7	42.9	43.9	44.5	38.8	39.4	40.5	41.7	42.9	43.9	44.5
Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
50th	90	90	91	92	93	94	94	48	49	49	50	51	52	52
90th	102	103	104	105	105	106	107	60	61	62	62	63	64	64
95th	107	107	108	108	109	110	110	63	64	65	66	67	67	68
95th + 12 mmHg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5 years														
Height (in)	41.1	41.8	43.0	44.3	45.5	46.7	47.4	41.1	41.8	43.0	44.3	45.5	46.7	47.4
Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
50th	91	92	93	94	95	96	96	51	51	52	53	54	55	55
90th	103	104	105	106	107	108	108	63	64	65	65	66	67	67
95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
95th + 12 mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6 years														
Height (in)	43.4	44.2	45.4	46.8	48.2	49.4	50.2	43.4	44.2	45.4	46.8	48.2	49.4	50.2
Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
50th	93	93	94	95	96	97	98	54	54	55	56	57	57	58
90th	105	105	106	107	109	110	110	66	66	67	68	68	69	69
95th	108	109	110	111	112	113	114	69	70	70	71	72	72	73
95th + 12 mmHg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7 years														
Height (in)	45.7	46.5	47.8	49.3	50.8	52.1	52.9	45.7	46.5	47.8	49.3	50.8	52.1	52.9
Height (cm)	116.1	118.0	121.4	125.1	128.9	132.4	134.5	116.1	118.0	121.4	125.1	128.9	132.4	134.5
50th	94	94	95	97	98	98	99	56	56	57	58	58	59	59
90th	106	107	108	109	110	111	111	68	68	69	70	70	71	71
95th	110	110	111	112	114	115	116	71	71	72	73	73	74	74
95th + 12 mmHg	122	122	123	124	126	127	128	83	83	84	85	85	86	86
8 years														
Height (in)	47.8	48.6	50.0	51.6	53.2	54.6	55.5	47.8	48.6	50.0	51.6	53.2	54.6	55.5
Height (cm)	121.4	123.5	127.0	131.0	135.1	138.8	141.0	121.4	123.5	127.0	131.0	135.1	138.8	141.0
50th	95	96	97	98	99	99	100	57	57	58	59	59	60	60
90th	107	108	109	110	111	112	112	69	70	70	71	72	72	73
95th	111	112	112	114	115	116	117	72	73	73	74	75	75	75
95th + 12 mmHg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9 years														
Height (in)	49.6	50.5	52.0	53.7	55.4	56.9	57.9	49.6	50.5	52.0	53.7	55.4	56.9	57.9
Height (cm)	126.0	128.3	132.1	136.3	140.7	144.7	147.1	126.0	128.3	132.1	136.3	140.7	144.7	147.1
50th	96	97	98	99	100	101	101	57	58	59	60	61	62	62
90th	107	108	109	110	112	113	114	70	71	72	73	74	74	74
95th	112	112	113	115	116	118	119	74	74	75	76	76	77	77
95th + 12 mmHg	124	124	125	127	128	130	131	86	86	87	88	88	89	89
10 years														
Height (in)	51.3	52.2	53.8	55.6	57.4	59.1	60.1	51.3	52.2	53.8	55.6	57.4	59.1	60.1
Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	145.9	150.1	152.7
50th	97	98	99	100	101	102	103	59	60	61	62	63	63	64
90th	108	109	111	112	113	115	116	72	73	74	74	75	75	76
95th	112	113	114	116	118	120	121	76	76	77	77	78	78	78
95th + 12 mmHg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11 years														
Height (in)	53.0	54.0	55.7	57.6	59.6	61.3	62.4	53.0	54.0	55.7	57.6	59.6	61.3	62.4
Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
50th	99	99	101	102	103	104	106	61	61	62	63	63	63	63
90th	110	111	112	114	116	117	118	74	74	75	75	75	76	76
95th	114	114	116	118	120	123	124	77	78	78	78	78	78	78
95th + 12 mmHg	126	126	128	130	132	135	136	89	90	90	90	90	90	90

12 years														
Height (in)	55.2	56.3	58.1	60.1	62.2	64.0	65.2	55.2	56.3	58.1	60.1	62.2	64.0	65.2
Height (cm)	140.3	143.0	147.5	152.7	157.9	162.6	165.5	140.3	143.0	147.5	152.7	157.9	162.6	165.5
50th	101	101	102	104	106	108	109	61	62	62	62	62	63	63
90th	113	114	115	117	119	121	122	75	75	75	75	75	76	76
95th	116	117	118	121	124	126	128	78	78	78	78	78	79	79
95th + 12 mmHg	128	129	130	133	136	138	140	90	90	90	90	90	91	91
13 years														
Height (in)	57.9	59.1	61.0	63.1	65.2	67.1	68.3	57.9	59.1	61.0	63.1	65.2	67.1	68.3
Height (cm)	147.0	150.0	154.9	160.3	165.7	170.5	173.4	147.0	150.0	154.9	160.3	165.7	170.5	173.4
50th	103	104	105	108	110	111	112	61	60	61	62	63	64	65
90th	115	116	118	121	124	126	126	74	74	74	75	76	77	77
95th	119	120	122	125	128	130	131	78	78	78	78	80	81	81
95th + 12 mmHg	131	132	134	137	140	142	143	90	90	90	90	92	93	93
14 years														
Height (in)	60.6	61.8	63.8	65.9	68.0	69.8	70.9	60.6	61.8	63.8	65.9	68.0	69.8	70.9
Height (cm)	153.8	156.9	162.0	167.5	172.7	177.4	180.1	153.8	156.9	162.0	167.5	172.7	177.4	180.1
50th	105	106	109	111	112	113	113	60	60	62	64	65	66	67
90th	119	120	123	126	127	128	129	74	74	75	77	78	79	80
95th	123	125	127	130	132	133	134	77	78	79	81	82	83	84
95th + 12 mmHg	135	137	139	142	144	145	146	89	90	91	93	94	95	96
15 years														
Height (in)	62.6	63.8	65.7	67.8	69.8	71.5	72.5	62.6	63.8	65.7	67.8	69.8	71.5	72.5
Height (cm)	159.0	162.0	166.9	172.2	177.2	181.6	184.2	159.0	162.0	166.9	172.2	177.2	181.6	184.2
50th	108	110	112	113	114	114	114	61	62	64	65	66	67	68
90th	123	124	126	128	129	130	130	75	76	78	79	80	81	81
95th	127	129	131	132	134	135	135	78	79	81	83	84	85	85
95th + 12 mmHg	139	141	143	144	146	147	147	90	91	93	95	96	97	97
16 years														
Height (in)	63.8	64.9	66.8	68.8	70.7	72.4	73.4	63.8	64.9	66.8	68.8	70.7	72.4	73.4
Height (cm)	162.1	165.0	169.6	174.6	179.5	183.8	186.4	162.1	165.0	169.6	174.6	179.5	183.8	186.4
50th	111	112	114	115	115	116	116	63	64	66	67	68	69	69
90th	126	127	128	129	131	131	132	77	78	79	80	81	82	82
95th	130	131	133	134	135	136	137	80	81	83	84	85	86	86
95th + 12 mmHg	142	143	145	146	147	148	149	92	93	95	96	97	98	98
17 years														
Height (in)	64.5	65.5	67.3	69.2	71.1	72.8	73.8	64.5	65.5	67.3	69.2	71.1	72.8	73.8
Height (cm)	163.8	166.5	170.9	175.8	180.7	184.9	187.5	163.8	166.5	170.9	175.8	180.7	184.9	187.5
50th	114	115	116	117	117	118	118	65	66	67	68	69	70	70
90th	128	129	130	131	132	133	134	78	79	80	81	82	82	83
95th	132	133	134	135	137	138	138	81	82	84	85	86	86	87
95th + 12 mmHg	144	145	146	147	149	150	150	93	94	96	97	98	98	99

The 50th, 90th, and 95th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile). BP stages are defined as elevated BP ≥90th percentile but <95th percentile; stage 1 HTN: ≥95th percentile or 130/80 to 139/89 mmHg; and stage 2 HTN: ≥95th percentile + 12 mmHg or >140/90 mmHg.

BP: blood pressure; BMI: body mass index; HTN: hypertension.

SCREENING OF BP recommendations:

- For children without risk factors or conditions associated with HTN, BP is measured beginning at three years of age during annual health supervision visits.
- For children ≥3 years of age with risk factors for HTN, BP measurement is recommended at every health care encounter .
- Children <3 years of age with risk factors for HTN should have BP measurements taken at each health supervision .
- **>>**Children with systolic BP (SBP) or diastolic BP (DBP) that exceeds screening thresholds for age and sex require further evaluation, starting with repeat BP measurement.

Risk factors for hypertension in children ≥3 years

Check BP at all health encounters for children with the following:*
Obesity
Type 1 or type 2 diabetes
Renal disease
History of aortic arch obstruction or coarctation
Treatment with or taking drugs known to increase blood pressure: ▪ Decongestants ▪ Caffeine ▪ Nonsteroidal anti-inflammatory drugs ▪ Glucocorticoids ▪ Stimulants ▪ Hormonal contraception ▪ Tricyclic antidepressants ▪ Amphetamines ▪ Cocaine

BP: blood pressure.

* For children without risk factors, BP should be measured annually at health supervision visits beginning at age 3 years.

Risk factors for hypertension in children <3 years

Check BP at health supervision visits for children with the following:*
Perinatal risk factors: ▪ Born at <32 weeks gestation ▪ Small for gestational age ▪ Birth weight <1500 g ▪ Neonatal complications that required intensive care or umbilical artery catheterization
Recurrent urinary tract infection, hematuria, or proteinuria
Renal disease or urologic malformation
Family history of congenital renal disease
Solid organ or hematopoietic cell transplant
Malignancy or other systemic illness associated with hypertension (eg, neurofibromatosis, tuberous sclerosis complex, sickle cell disease)
Treatment with drugs known to raise blood pressure (eg, caffeine, nonsteroidal anti-inflammatory drugs, glucocorticoids)
Evidence of elevated intracranial pressure

Screening blood pressure requiring further evaluation

Age (years)	BP (mmHg)			
	Boys		Girls	
	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

This table is designed as a screening tool only for the identification of children and adolescents who need further evaluation of their BP, starting with repeat BP measurements. The table should not be used by itself to diagnose elevated BP or hypertension. Refer to UpToDate content on hypertension in children for additional details.

BP: blood pressure.

MEASUREMENT OF BLOOD PRESSURE

- The diagnosis of HTN is dependent on accurate blood pressure (BP) measurement. If a high BP measurement is obtained by an oscillometric device, confirmation by ausculatory measurement is required for accuracy.

- The variability of BP values due to procedural differences in the BP measurement was illustrated in a comparison of normal BP readings reported by 10 different investigators in which the BP values differed by as much as 20 mmHg . Confounding factors included **cuff size**, **technique used** (ie, patient position and the choice of fourth or fifth Korotkoff sound to determine diastolic BP [DBP]), **the number of measurements made**, and/or **type of instruments used**.

- Cuff size and placement — A variety of different cuff sizes are available, including adult, large adult, and thigh cuffs. **The correct choice of cuff is important for accurate BP measurement**. If too small a cuff is used, the pressure generated by inflating the cuff may not be fully transmitted to the brachial artery. In this setting, the pressure in the cuff may be considerably higher than the intra-arterial pressure, leading to overestimation of the systolic pressure. On the other hand, too wide a cuff may produce lower readings than the actual intra-arterial pressure.

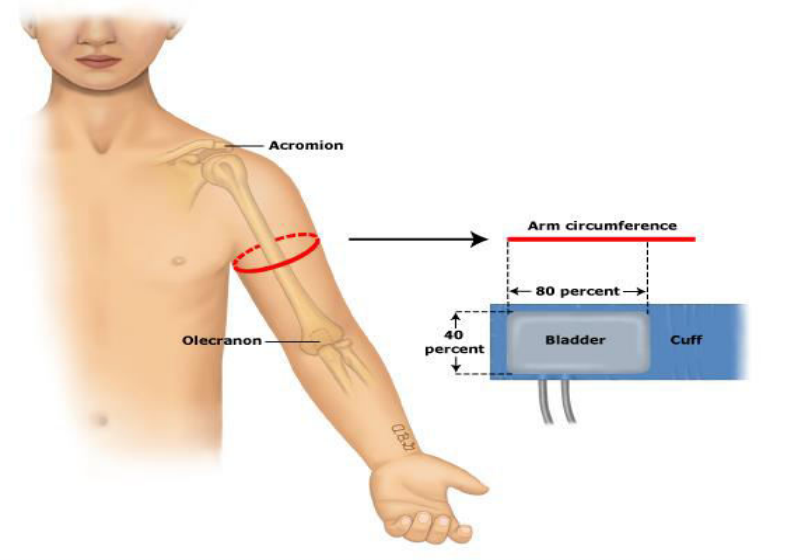
- The cuff size should have a bladder width that is approximately 40 percent of the circumference of the upper arm, measured midway between the olecranon and the acromion. The length of the cuff bladder should encircle 80 to 100 percent of the circumference of the upper arm midway between the olecranon and the acromion. The bladder width-to-length should be at least 1:2.

TABLE 2. Recommended Dimensions for BP Cuff Bladders

Age Range	Width, cm	Length, cm	Maximum Arm Circumference, cm*
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small adult	10	24	26
Adult	13	30	34
Large adult	16	38	44
Thigh	20	42	52

* Calculated so that the largest arm would still allow the bladder to encircle arm by at least 80%.

Determining appropriate blood pressure cuff size in children



The width of the bladder of the blood pressure cuff should be approximately 40 percent of the circumference of the upper arm midway between the olecranon and the acromion. The length of the bladder of the cuff should encircle 80 to 100 percent of the circumference of the upper arm at the same position.

UpToDate

- **Auscultation**

- The preferred method of BP measurement is auscultation using a mercury sphygmomanometer as this was how normative data were obtained . The mercury sphygmomanometer is the most accurate instrument, but its availability is restricted because of the potential risk of mercury poisoning.
- Aneroid sphygmomanometers are an appropriate substitute for mercury-containing devices and have been shown to be accurate if regularly calibrated against mercury sphygmomanometers
- The following steps are recommended to accurately measure BP by auscultation and compare values with normative data :

✓ **Prior to BP measurement, stimulant drugs or food should be avoided.**

✓ **The BP should be measured after three to five minutes of rest in a quiet environment**. The child should be seated with his/her back and feet in a supported position. In infants, BP is measured in a supine position.

✓ **Measure BP when the heart rate is normal and steady to minimize the likelihood of obtaining falsely elevated readings.** Because anxiety acutely raises both the heart rate and BP, the most reproducible readings are obtained when the pulse rate is both steady and within the normal range.

✓ **The BP is measured by auscultation using the correct size and placement of the BP cuff, and by placing the bell of the stethoscope over the brachial artery pulse in the cubital fossa** . The BP should be taken with the patient's right arm supported at the level of the heart. The right arm is preferred in repeated measures of BP for consistency and comparison with standard tables. In addition, the possibility of coarctation of the aorta would lead to falsely low BP readings in the left arm. Allowing the arm to hang below the heart will elevate BP levels by the added hydrostatic pressure induced by gravity (as much as 10 to 12 mmHg in adults) . The sphygmomanometer should be visible but does not have to be at the level of the heart .

✓ The cuff should be inflated to 20 to 30 mmHg above the anticipated systolic BP (SBP) and then deflated slowly at a rate of 2 to 3 mmHg per heartbeat. The systolic BP is equal to the pressure at which the brachial pulse can first be heard by auscultation (Korotkoff phase I). As the cuff is deflated below the SBP, the pulse continues to be heard until there is abrupt muffling (Korotkoff phase IV) followed by disappearance of sound (Korotkoff phase V) .

✓ Phase V is recommended for DBP determination in children . In some children, Korotkoff sounds can be heard to 0 mmHg. If this occurs, BP measurement should be repeated with less pressure on the head of the stethoscope. If phase V is still very low, phase IV (muffling) should be recorded as the DBP with the added documentation noting the use of the phase IV to determine DBP.

- **Number of measurements**

- **The BP should be taken at least twice on each visit**, with the measurements separated by one to two minutes to allow the release of trapped blood. If the second value is more than 5 mmHg different from the first, continued measurements should be made until a stable value is attained. The recorded value on the patient's chart should be the average of the last two measurements.

- **A new diagnosis of HTN should not be made until the SBP and/or DBP measurement is ≥95th percentile or ≥130/80 mmHg on at least three separate visits.** Many children have substantial reductions in BP between the first and third visits. The fall in BP with serial measurements is primarily because of two factors: an accommodation effect resulting from reduced anxiety over time and regression to the mean

- **Oscillometric devices**

  - Automated oscillometric devices **measure mean arterial BP based upon pressure oscillations of the brachial artery wall as the cuff is deflated. SBP and DBP measurements are calculated based on the mean BP**. Manufacturers of oscillometric devices use different algorithms for these calculations.

  - Oscillometric devices are commonly used in practice because of their ease of use and decrease in observer bias . **They are particularly helpful when auscultation is difficult, as with infants and neonates; in the intensive care setting when frequent BP measurement is needed; or to screen initial BP in a busy clinical setting** . However, measurements obtained by oscillometric devices are usually higher compared with readings obtained by auscultation . As a result, we concur with the AAP recommendations that **BP readings ≥90th percentile obtained with an oscillometric device be confirmed by auscultation**

Limitations of oscillometric devices include:

- There is a wide range of BP values when different devices are compared, with 30 percent of SBP measurements varying by more than 10 mmHg .
- As noted above, oscillometric readings are generally higher when compared with auscultated BP measurements
- Oscillometric devices require maintenance and repeated calibration. .

- **AMBULATORY BP MEASUREMENTS**

  - Blood pressure (BP) changes continually in response to physiologic and environmental stimuli. In adults, 24-hour ambulatory blood pressure monitoring (ABPM) has had better reproducibility and better correlation with the risk of hypertensive cardiovascular (CV) complications and target-organ damage than office BP measurements.

  - Data are more limited in children, but also indicate an important role of ABPM in the evaluation of hypertension (HTN) . In particular, ABPM provides multiple measurements during regular activities and is the only method that allows BP measurement during sleep, and therefore is felt to provide a more accurate description of the patient's BP than office BP measurements. It is especially useful (and the only recommended method) to **identify white coat HTN in children who are anxious in the medical setting, as well as those with masked HTN with normal BP in the clinical setting and elevated BP by ABPM**. For these reasons, the use of ABPM has been advocated for in the evaluation of children who have elevated BP or are at risk for elevated BP

  - ABPM Definition of hypertension — Of note, **the threshold ambulatory blood pressure monitoring (ABPM) values used to diagnose HTN are higher than those used for casual/office thresholds, most likely because they use oscillometric technique and not auscultation and because BP is higher when individuals are active and/or ambulatory versus when they are at rest**. The correlation between

ABPM and office measurements is poor and normative data are limited. The normative data that are used in clinical practice are based on a single study of approximately 1000 Central European children and adolescents

24-hour ambulatory blood pressure (BP) levels for girls based on age

Age (years)	Average 24-hour BP (percentile)				Average day BP (percentile)				Average night BP (percentile)			
	50th	75th	90th	95th	50th	75th	90th	95th	50th	75th	90th	95th
5	103/66	108/69	112/72	115/74	108/73	114/77	118/80	121/82	95/56	100/61	105/66	108/69
6	104/66	109/69	114/72	116/74	110/73	115/77	120/80	122/82	96/56	101/61	106/65	110/68
7	105/66	110/69	115/72	118/74	111/72	116/77	121/80	123/82	96/56	102/60	107/65	111/67
8	107/66	112/69	116/72	119/74	112/72	117/76	122/80	124/82	97/55	103/60	108/64	112/67
9	108/66	113/70	117/73	120/74	112/72	118/76	122/80	125/82	98/55	103/59	109/64	112/67
10	109/66	114/70	118/73	121/75	113/72	119/76	123/79	126/81	98/55	104/59	110/64	113/67
11	110/66	115/70	119/73	122/75	114/72	120/76	124/79	127/81	99/54	105/59	110/63	114/66
12	111/67	116/70	120/74	123/76	115/72	121/76	125/80	128/82	100/54	105/59	110/63	114/66
13	112/67	117/71	121/74	124/76	116/72	122/77	126/80	129/82	101/54	106/59	111/63	114/66
14	113/67	118/71	122/74	125/76	118/73	123/77	127/80	130/82	101/55	106/59	111/63	114/65
15	114/68	118/71	123/75	125/77	119/73	124/77	128/80	130/82	102/55	107/59	111/63	114/65
16	115/68	119/71	123/75	126/77	120/74	124/77	129/80	131/82	103/55	107/59	111/63	114/65

The values are in mmHg and are the average BP based on 24-hour ambulatory BP monitoring.

24-hour ambulatory blood pressure (BP) levels for girls based on height

Height (cm)	Average 24-hour BP (percentile)				Average day BP (percentile)				Average night BP (percentile)			
	50th	75th	90th	95th	50th	75th	90th	95th	50th	75th	90th	95th
120	104/66	108/69	112/71	114/72	110/73	114/77	118/80	120/82	95/55	99/60	103/63	106/65
125	105/66	109/69	113/71	116/73	111/73	115/77	119/80	121/82	96/55	100/60	104/63	107/66
130	106/66	110/69	114/72	117/73	111/72	116/76	120/80	122/82	96/55	101/59	106/63	108/66
135	107/66	111/70	115/72	118/74	112/72	116/76	120/80	123/82	97/55	102/59	107/63	109/66
140	108/66	112/70	116/73	119/75	112/72	117/76	121/80	124/82	98/55	103/59	108/63	110/66
145	109/66	113/70	117/73	120/75	113/72	118/76	123/80	125/82	98/54	103/59	109/63	112/66
150	110/67	115/70	119/74	121/76	114/72	119/76	124/80	127/82	99/54	104/59	110/63	113/66
155	111/67	116/71	120/74	123/76	116/72	121/76	125/80	128/82	100/54	106/59	111/63	114/66
160	112/67	117/71	121/74	123/76	117/72	122/76	126/80	129/82	101/55	106/59	111/63	114/66
165	114/67	118/71	122/74	124/76	118/73	123/77	127/80	130/82	102/55	107/59	112/63	114/66
170	115/68	119/71	123/74	125/76	120/74	124/77	128/80	131/82	103/55	108/61	112/67	115/71
175	116/69	120/72	124/75	126/76	121/75	125/78	129/81	131/82	105/55	109/59	113/63	115/66

The values are in mmHg and are the average BP based on 24-hour ambulatory BP monitoring.

- Pre-hypertension – Office systolic BP (SBP) or diastolic BP (DBP) >90th to <95th percentile, mean ambulatory SBP or DBP <95th percentile, and ambulatory SBP or DBP load of 25 to 50 percent.
- Ambulatory hypertension – Office BP >95th percentile, mean ambulatory SBP or DBP >95th percentile and SBP or DBP load of 25 to 50.

- **FOLLOW-UP**

- The decision process for follow-up, evaluation, and treatment varies with the elevation of BP . Stage 2 HTN identifies those children who need more prompt evaluation and, depending on end-organ damage and or clinical presentation, potentially immediate pharmacologic treatment. As a result**, the timing of repeat blood pressure (BP) measurements is dependent upon the initial level of elevated BP, and if there are symptoms associated with HTN**

- **Elevated BP** – For children with elevated BP documented by auscultatory measurements, nonpharmacologic therapy (ie, lifestyle changes) is recommended and BP should be rechecked by auscultation in six months.

- If BP remains elevated after six months, upper and lower extremity BP should be checked (right arm, left arm, and one leg) to detect coarctation of the aorta, lifestyle counseling is repeated, and auscultated BP is rechecked in six months.

- If BP continues at the elevated BP level after 12 months (eg, after three auscultatory measurements), ambulatory blood pressure monitoring (ABPM) should be considered, and diagnostic evaluation should be considered if appropriate. Consider subspecialty referral (ie, nephrology or cardiology). If ABPM is not available, home BP readings with appropriate training and blood pressure cuff may be considered to help with further management decisions.

- If BP normalizes at any point, return to annual BP screening at health supervisory care visits.

- **Stage 1 HTN**

- Provide recommendations for nonpharmacologic measures and recheck within one to two weeks (or sooner if the patient is symptomatic). If BP remains elevated, upper and lower extremity BP should be checked (right arm, left arm, and one leg) to detect coarctation of the aorta, and BP should be rechecked in three months by auscultation. If BP remains at the stage 1 level, ABPM should be ordered (if available), and diagnostic evaluation should be considered if appropriate. Consider subspecialty referral (ie, nephrology or cardiology).

- **Stage 2 HTN**

- If the patient is symptomatic, the BP is >30 mmHg above the 95th percentile, or >180/120 mmHg (whichever is lower), the child should be referred for immediate care
- If the patient is not symptomatic, upper and lower extremity BP should be checked to detect coarctation of the aorta (right arm, left arm, and one leg), lifestyle recommendations given, and the BP measurement should be repeated within one week. Alternatively, the patient could be referred to subspecialist with expertise in the evaluation and management of elevated pediatric blood pressure within one week. If at the next visit the BP is still at the stage 2 level, diagnostic evaluation, including ABPM and treatment by a specialist should be considered.

- **Types, Causes & Clinical Picture of Hypertension**

- It's Either **Primary (Essential) HTN** or **Secondary HTN**

- **Secondary HTN**

✓ **More common in pediatric age groups**

✓ **Usualy there is an underlying condition that causes elevated BP**

✓ **Pt's will have elevated BP Levels ranging from mild to severe**

✓ Pt's With Secondary HTN vary in **presentation**:

1) They are either Asymptomatic or symptoms of the underlying causative disease process (e.g. Growth failure in CKD)

2) Presents with headache, dizziness, epistaxis, anorexia, visual changes, and seizures may occur.

3) Hypertensive encephalopathy (suggested by the presence of vomiting, temperature elevation, ataxia, stupor, CT abnormalities, and seizures).

- **When to suspect secondary HTN**

- A very young child (<10 years).
- Higher BP readings.
- No family history of HTN.
- presence of symptoms related to hypertension.
- Poor response to treatment (suspect non-compliance!)

- **Causes…**

1. **Renal (Mostly, 90% due to renovascular causes)**
2. **Cardiac**
3. **Vascular**
4. **Endocrine**
5. **Neurological**
6. **Drugs**
7. **Others**

Table 166-1. Causes of Hypertension

Renal Causes
Congenital anomalies
Dysplastic kidney
Polycystic kidney
Obstructive uropathy
Acquired Lesions
Wilms tumor
Glomerulonephritis
Hemolytic uremic syndrome
Reflux nephropathy
Drugs, toxins
Systemic lupus erythematosus
Endocrine Causes

Vascular Causes
Coarctation of the aorta
Renal artery embolism
Renal vein thrombosis
Renal artery stenosis
Arteritis (Takayasu, periarteritis nodosa)
Neurologic Causes
Guillain-Barré syndrome
Dysautonomia (Riley-Day syndrome)
Increased intracranial pressure
Quadriplegia
Stress, anxiety
Sympathomimetic drugs
Poliomyelitis
Encephalitis
Neurofibromatosis

TABLE 3
Causes of Childhood Hypertension According to Age Group

Age	*Causes*
One to six years	Renal parenchymal disease; renal vascular disease; endocrine causes; coarctation of the aorta; essential hypertension
Six to 12 years	Renal parenchymal disease; essential hypertension; renal vascular disease; endocrine causes; coarctation of the aorta; iatrogenic illness
12 to 18 years	Essential hypertension; iatrogenic illness; renal parenchymal disease; renal vascular disease; endocrine causes; coarctation of the aorta

- **Primary (Essential) HTN**

✓ No identifiable cause can be found.
✓ Less common than Secondary HTN.

- usually characterized by mild or Stage 1 hypertension.

✓ Hereditary factors, Diet, Stress and Obesity Plays a role in it's development

- associated with a positive family history of hypertension or cardiovascular disease (CVD).

✓ As the child Grows (school aged→ Adolescent) it becomes increasingly common
✓ Prevalence increases progressively with increasing body mass index (BMI >95%) 30% have HTN .

children and adolescents with primary (essential) hypertension are commonly overweight, often have a strong family history of hypertension, and usually have BP values at or only slightly above the 95th percentile for age.

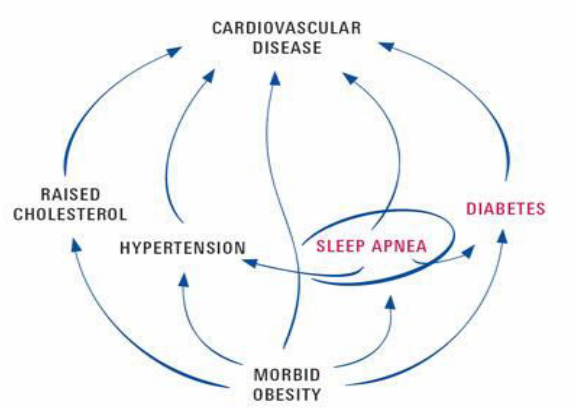
Overweight and high BP are components of the insulin-resistance syndrome (metabolic syndrome) that Further more exaggerated their individual CVS and diabetes risks.

- In a child with primary hypertension, the presence of any comorbidity that is associated with hypertension carries the potential to increase the risk for CVD and can have an adverse effect on health outcome.

There is an association Between sleep disorders and higher blood pressure in Children.

- Approximately 15 percent of children snore , and at least 1–3 percent have sleep-disordered breathing have elevated BP.

So Brief Sleep Hx should be obtained Using



(BEARS)

B: Bedtime problems,

E: Excessive daytime sleepiness

A: Awakenings during the night

R: Regularity and duration of sleep

S : Sleep-disordered breathing (snoring)

As Essential HTN is Asymptomatic, Doctors should always assess for Target Organ damage whenever they diagnose it.

- **Target-Organ Abnormalities in Childhood Hypertension**

Target-organ abnormalities are commonly associated with hypertension in children and adolescents.

1. Left ventricular hypertrophy (LVH) is the most prominent evidence of target-organ damage.

- LVH has been reported in 34–38 percent of children and adolescents with mild, untreated BP elevation.
  Pediatric patients with established Hypertension should have echocardiographic assessment of left ventricular mass at diagnosis and periodically thereafter.
- The presence of LVH is an indication to Initiate Or intensify antihypertensive therapy

2. hypertensive retinopathy .
3. Renal damage .
4.atherosclorsis

- At the present time, additional testing for other target-organ abnormalities (such as determination of carotid intimal-medial thickness and evaluation of urine for microalbuminuria) is not recommended for routine clinical use.

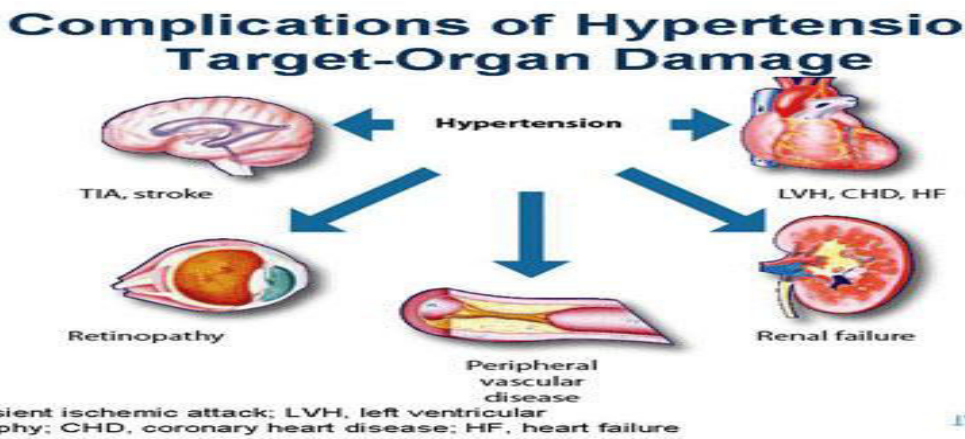


Table 1. Target-Organ Damage Caused by Systemic Hypertension

Target Organ	Target-Organ Damage	Appropriate Assessment Tests
Brain	• Depression • Seizures	Complete neurologic examination
Eyes	• Retinal detachment • Hemorrhage • Vessel tortuosity	Complete ocular examination (See **Ten Tips to Improve Your Ophthalmology Skills**, July/ August 2011)
Heart & blood vessels	• Left ventricular hypertrophy • Congestive heart failure	Auscultation, ECG, thoracic radiographs, cardiac ultrasound
Kidney	• Renal azotemia • Proteinuria	Blood creatinine, urine protein:creatinine ratio

ECG = electrocardiogram

- **History and physical examination**
  - **History**
    - ❑ A well-taken history provides clues about the cause of hypertension and guides the selection and sequencing of the following investigations.
    - ❑ Presenting symptoms and signs are not specific in neonates and are absent in most older children unless the hypertension is severe.
    - ❑ Relevant information includes the following:
      - Prematurity.
      - Bronchopulmonary dysplasia.
      - History of umbilical artery catheterization. (may cause renal artery clot)
      - Failure to thrive.
      - History of head or abdominal trauma.
      - Family history of heritable diseases. (eg, neurofibromatosis, hypertension)
      - History
      - Medications. (eg, pressor substances, steroids, tricyclic antidepressants, cold remedies, medications for attention deficit hyperactivity disorder [ADHD])
      - Episodes of pyelonephritis (perhaps suggested by unexplained fevers) that may result in renal scarring.
      - Dietary history, including caffeine, licorice, and salt consumption.

- Sleep history, especially snoring history.
- Habits, such as smoking, drinking alcohol, and ingesting illicit substances.
- History

❑ Signs and symptoms that should alert the physician to the possibility of hypertension in neonates include the following:

- Seizure.
- Irritability or lethargy.
- Respiratory distress.
- Congestive heart failure.
- History

❑ Signs and symptoms that should alert the physician to the possibility of hypertension in older children include all of the above, as well as the following:

- Headache.
- Fatigue.
- Blurred vision.
- Epistaxis.
- Bell palsy.
- Physical Examination

❑ A primary objective of the physical examination is to identify signs of secondary hypertension.

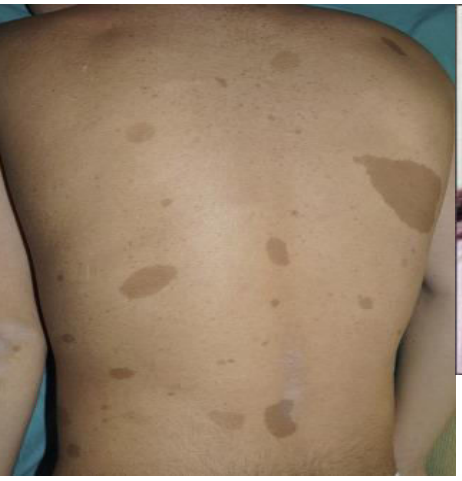
❑ The child's height, weight, and percentiles for age (growth parameters) should be determined at the start of the physical examination.

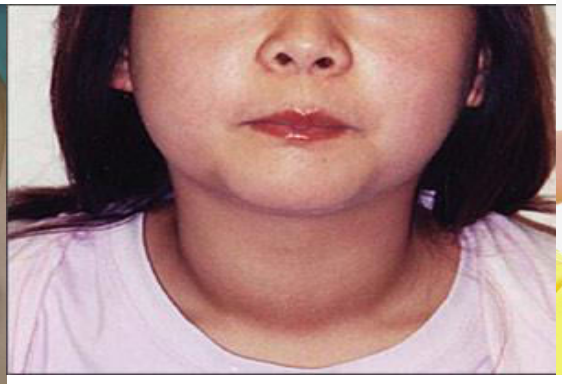
❑ When hypertension is confirmed, BP should be measured in both arms and in both legs.

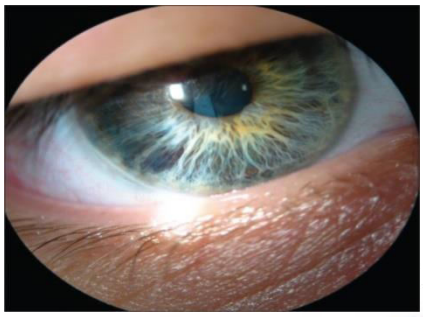
- **Physical Examination**

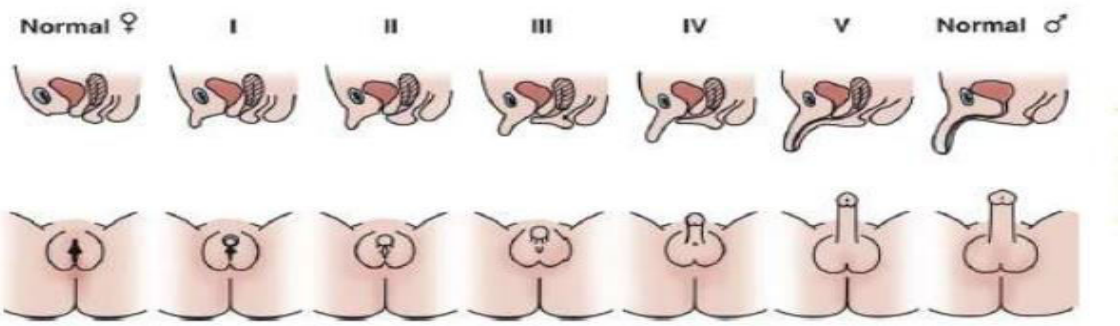
❑ The following should be evaluated to assess for potential causes of the hypertension:

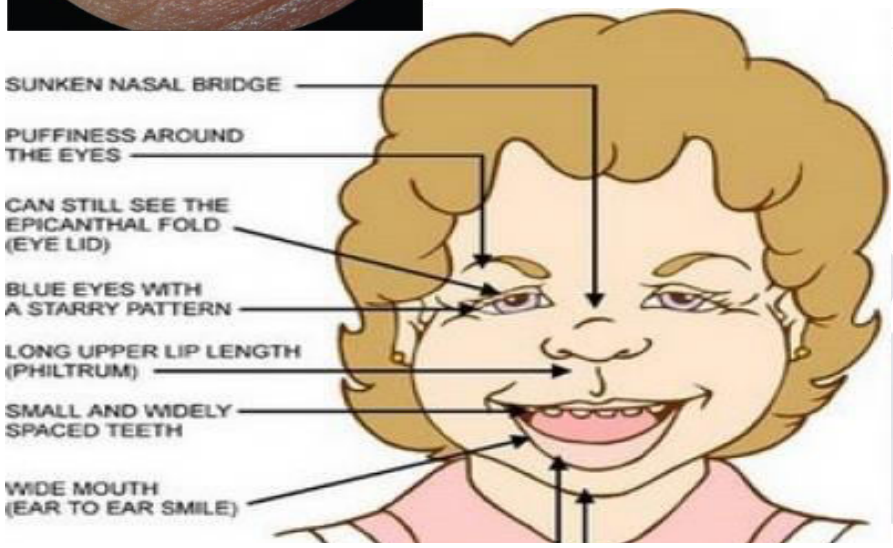
- Body mass index may lead to an evaluation for metabolic syndrome.
- Tachycardia may indicate hyperthyroidism, pheochromocytoma, and neuroblastoma.
- Growth retardation may suggest chronic renal failure.
- Café au lait spots may point to neurofibromatosis.
- An abdominal mass may lead to an evaluation for Wilms tumor and polycystic kidney disease.
- Physical Examination
- Epigastric or abdominal bruit may lead to the diagnosis of coarctation of the abdominal aorta or renal artery stenosis.
- BP difference between the upper and lower extremities indicates coarctation of the thoracic or abdominal aorta.
- Thyromegaly may suggest hyperthyroidism.
- Virilization or ambiguity may suggest adrenal hyperplasia.
- Stigmata of von Hippel-Lindau, Williams, or Turner syndromes.
- Acanthosis nigricans may indicate metabolic syndrome.

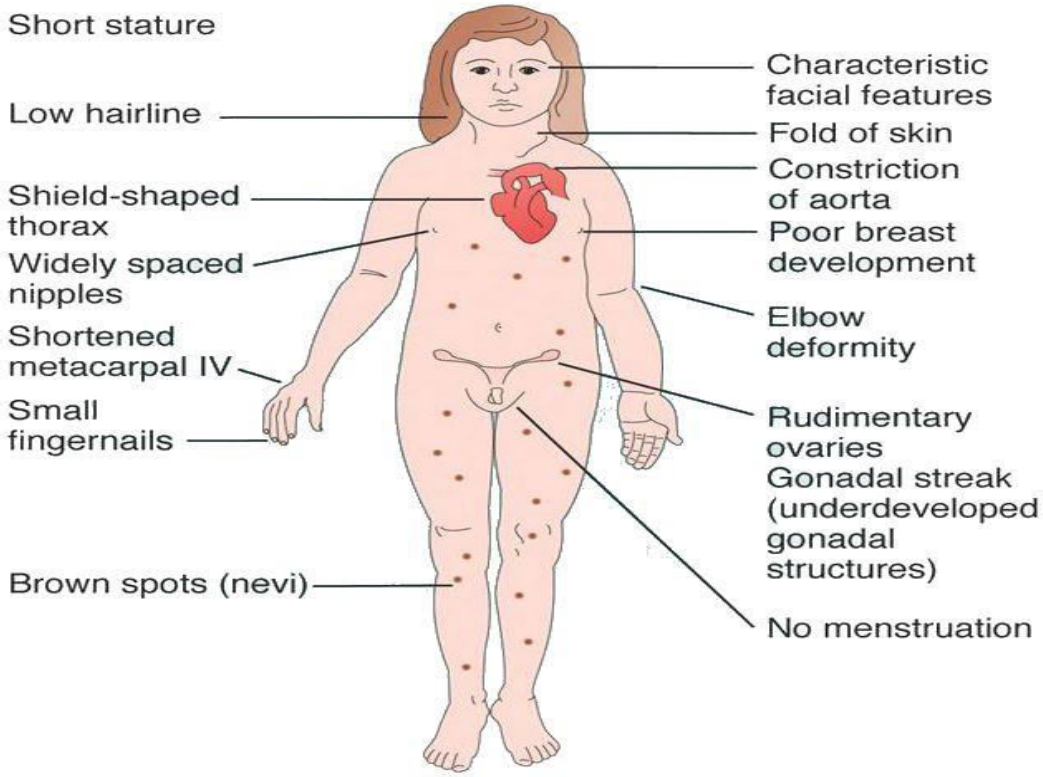







Normal ♀
I
II
III
IV
V
Normal ♂


SUNKEN NASAL BRIDGE
PUFFINESS AROUND THE EYES
CAN STILL SEE THE EPICANTHAL FOLD (EYE LID)
BLUE EYES WITH A STARRY PATTERN
LONG UPPER LIP LENGTH (PHILTRUM)
SMALL AND WIDELY SPACED TEETH
WIDE MOUTH (EAR TO EAR SMILE)


Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small fingernails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation

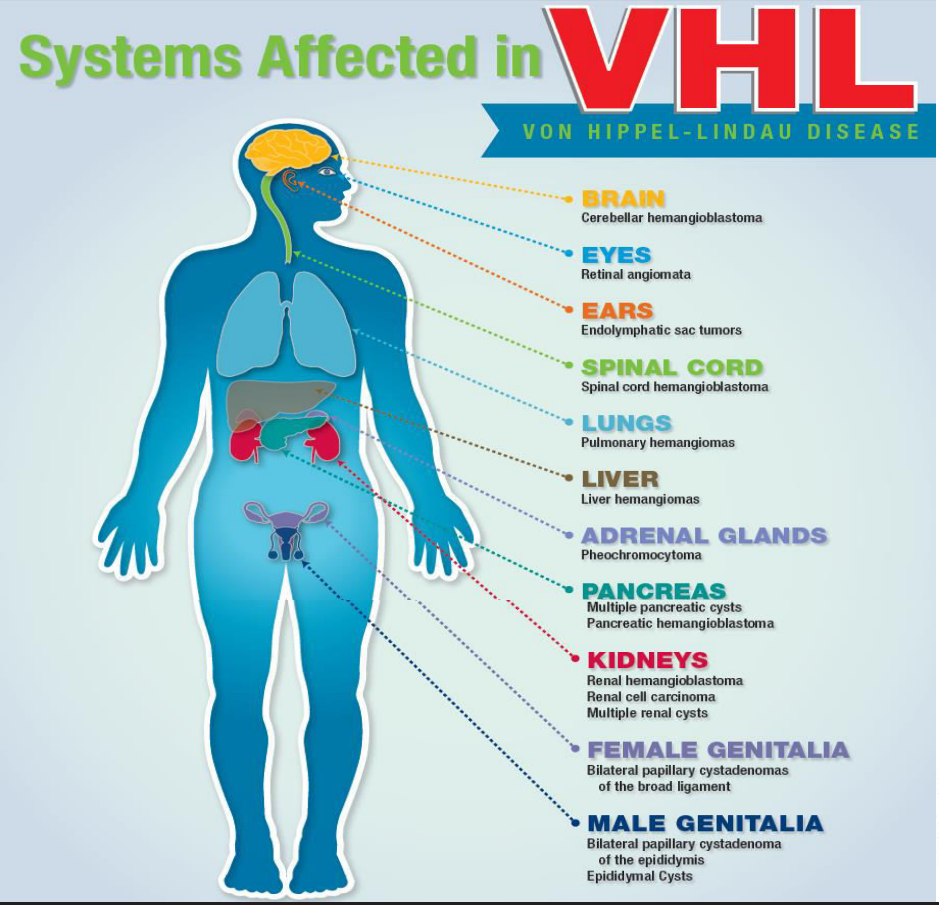
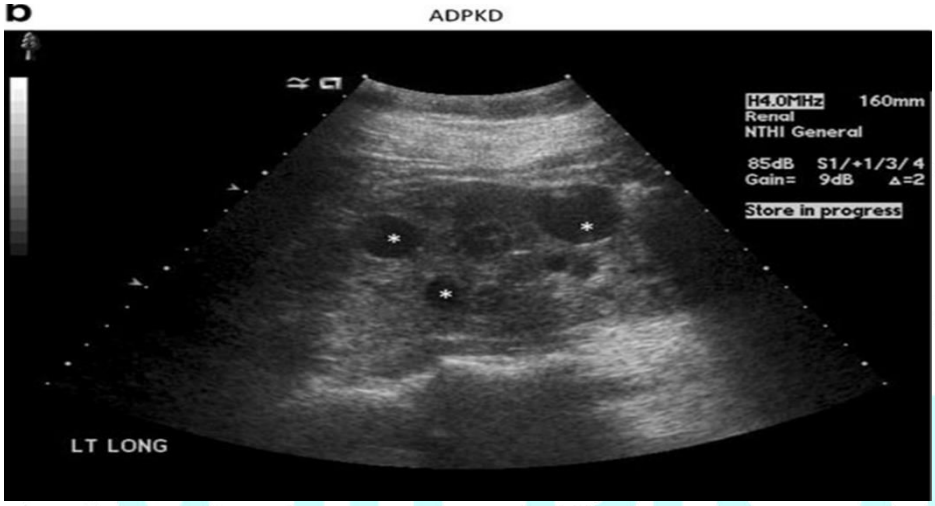


Table 445-4 Findings to Look for on Physical Examination in Patients with Hypertension

PHYSICAL FINDINGS	POTENTIAL RELEVANCE
GENERAL	
Pale mucous membranes, edema, growth retardation	Chronic renal disease
Elfin facies, poor growth, retardation	Williams syndrome
Webbing of neck, low hairline, widespread nipples, wide carrying angle	Turner syndrome
Moon face, buffalo hump, hirsutism, truncal obesity, striae, acne	Cushing syndrome
HABITUS	
Thinness	Pheochromocytoma, renal disease, hyperthyroidism
Virilization	Congenital adrenal hyperplasia
Rickets	Chronic renal disease
SKIN	
Café-au-lait spots, neurofibromas	Neurofibromatosis, pheochromocytoma
Tubers, "ash-leaf" spots	Tuberous sclerosis
Rashes	Systemic lupus erythematosus, vasculitis (Henoch-Schönlein purpura), impetigo with acute nephritis
Pallor, evanescent flushing, sweating	Pheochromocytoma
Needle tracks	Illicit drug use
Bruises, striae	Cushing syndrome
Acanthosis nigricans	Type 2 diabetes, insulin resistance
EYES	
Extraocular muscle palsy	Nonspecific, chronic, severe
Fundal changes	Nonspecific, chronic, severe
Proptosis	Hyperthyroidism
HEAD AND NECK	
Goiter	Thyroid disease
Adenotonsillar hypertrophy	Sleep disordered breathing
CARDIOVASCULAR SIGNS	
Absent of diminished femoral pulses, low leg pressure relative to arm pressure	Aortic coarctation
Heart size, rate, rhythm; murmurs; respiratory difficulty, hepatomegaly	Aortic coarctation, congestive heart failure
Bruits over great vessels	Arteritis or arteriopathy
Rub	Pericardial effusion secondary to chronic renal disease
PULMONARY SIGNS	
Pulmonary edema	Congestive heart failure, acute nephritis
Picture of bronchopulmonary dysplasia	Bronchopulmonary dysplasia-associated hypertension
ABDOMEN	
Epigastric bruit	Primary renovascular disease or in association with Williams syndrome, neurofibromatosis, fibromuscular dysplasia, or arteritis
Abdominal masses	Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidneys, hydronephrosis, dysplastic kidneys
NEUROLOGIC SIGNS	
Neurologic deficits	Chronic or severe acute hypertension with stroke
Muscle weakness	Hyperaldosteronism, Liddle syndrome
GENITALIA	
Ambiguous, virilized	Congenital adrenal hyperplasia

- **Investigations**

- **Basic Investigations**
  - CBC : R/O anemia, consistent with chronic renal disease.
  - BUN, creatinine, electrolytes, urinalysis and urine culture: R/O renal disease and chronic pyelonephritis.
  - Renal U/S : congenital anomaly, renal size.
  - Renal Doppler US.
  - Thyroid Function Test.
  - Echocardiogram(LVH).



- **Evaluation For comorbidity**
  - Fasting lipid panel, fasting glucose : hyperlipidemia and diabetes.
  - Drug screen : Identify substances that might cause hypertension. (amphetamines, Corticosteroids, decongestants)
  - Polysomnography : Identify sleep disorder, This test should be considered in obese children with a history of snoring, daytime sleepiness, or any sleep difficulties.

- **Evaluation For Target-Organ Damage**
  - Echocardiogram : Identify LVH and other indications of cardiac involvement, Left ventricular mass measurements should be indexed to height ($m^{2.7}$) to account for the effect of body size. The presence of LVH is an indication to treat the hypertension with pharmacologic therapy.
  - Left ventricular hypertrophy is detected in up to 40% of hypertensive children.
  - Other markers of target organ damage that have been demonstrated in hypertensive children include:

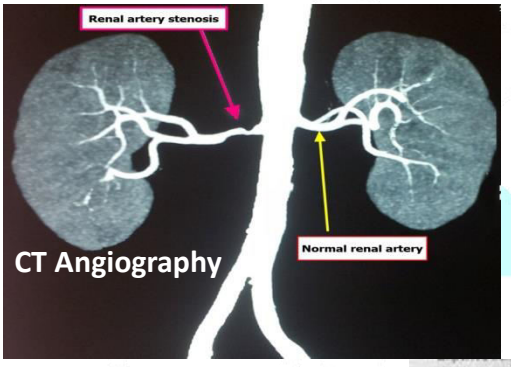
  increased carotid intima–media thickness, hypertensive retinopathy, and microalbuminuria.

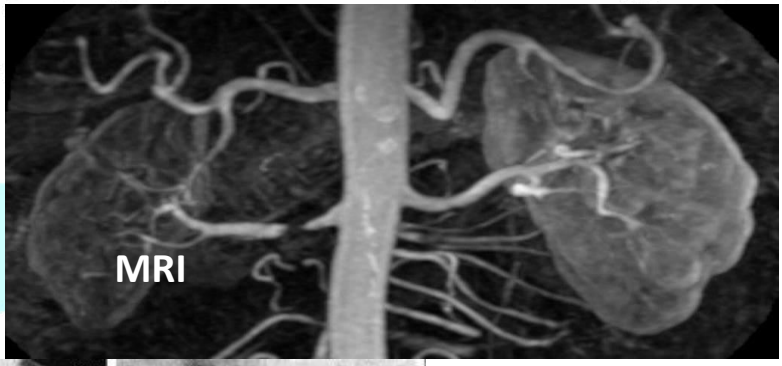
- **Further Evaluation As Indicated**
  - Ambulatory BP monitoring: Identify white-coat hypertension, also useful to recognize subjects at risk, and in evaluating response to treatment.
  - Plasma renin determination (Plasma Renin Activity): low renin activity suggesting mineralocorticoid-related disease, while high plasma renin activity indicates renal vascular hypertension, including coarctation of the aorta.

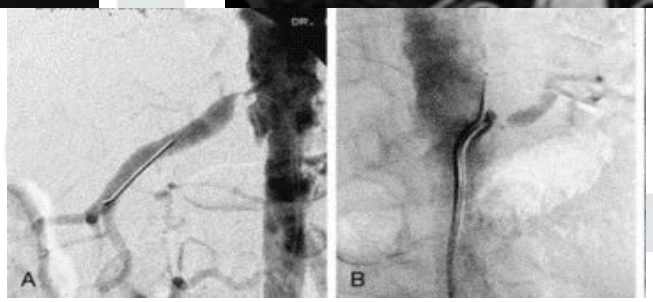
- Plasma and urine steroid levels (CAH) Identify steroid-mediated hypertension.
- Plasma and urine catecholamines (neuroblastoma) : Identify catecholamine-mediated hypertension.
- Urine sodium levels reflect dietary sodium intake and may be used as a marker to follow a patient after dietary changes are attempted.

- **For Renal Artery Stenosis**

- Isotope scintigraphy (renal scan).
- Magnetic resonance angiography.
- Duplex Doppler flow studies.
- 3-Dimensional CT.
- Arteriography: Digital subtraction angiography (DSA) or classic.
- Conformation by : angiography or CT angiography.
  (fluoroscopic angiography may be needed, especially to detect intrarenal arterial stenosis)







- **Secondary HTN-Screening Tests**

Diagnosis	Diagnostic Test
Chronic kidney disease	Estimated GFR
Coarctation of the aorta	CT angiography
Cushing's syndrome and other glucocorticoid excess states including chronic steroid therapy	History; dexamethasone suppression test
Drug induced/related (see table 18)	History; drug screening
Pheochromocytoma	24-hour urinary metanephrine and normetanephrine
Primary aldosteronism and other mineralocorticoid excess states	24-hour urinary aldosterone level or specific measurements of other mineralocorticoids
Renovascular hypertension	Doppler flow study; magnetic resonance angiography
Sleep apnea	Sleep study with O_2 saturation
Thyroid/parathyroid disease	TSH; serum PTH

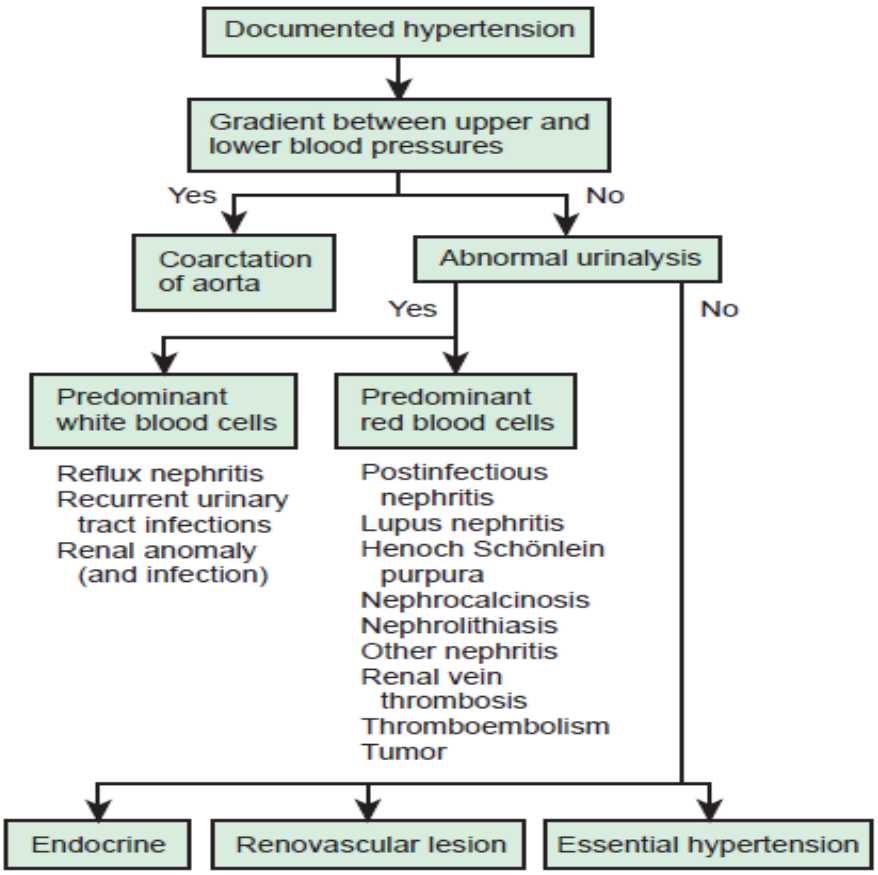


Figure 445-3 Initial diagnostic algorithm in the evaluation of hypertension. *(From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p. 222.)*

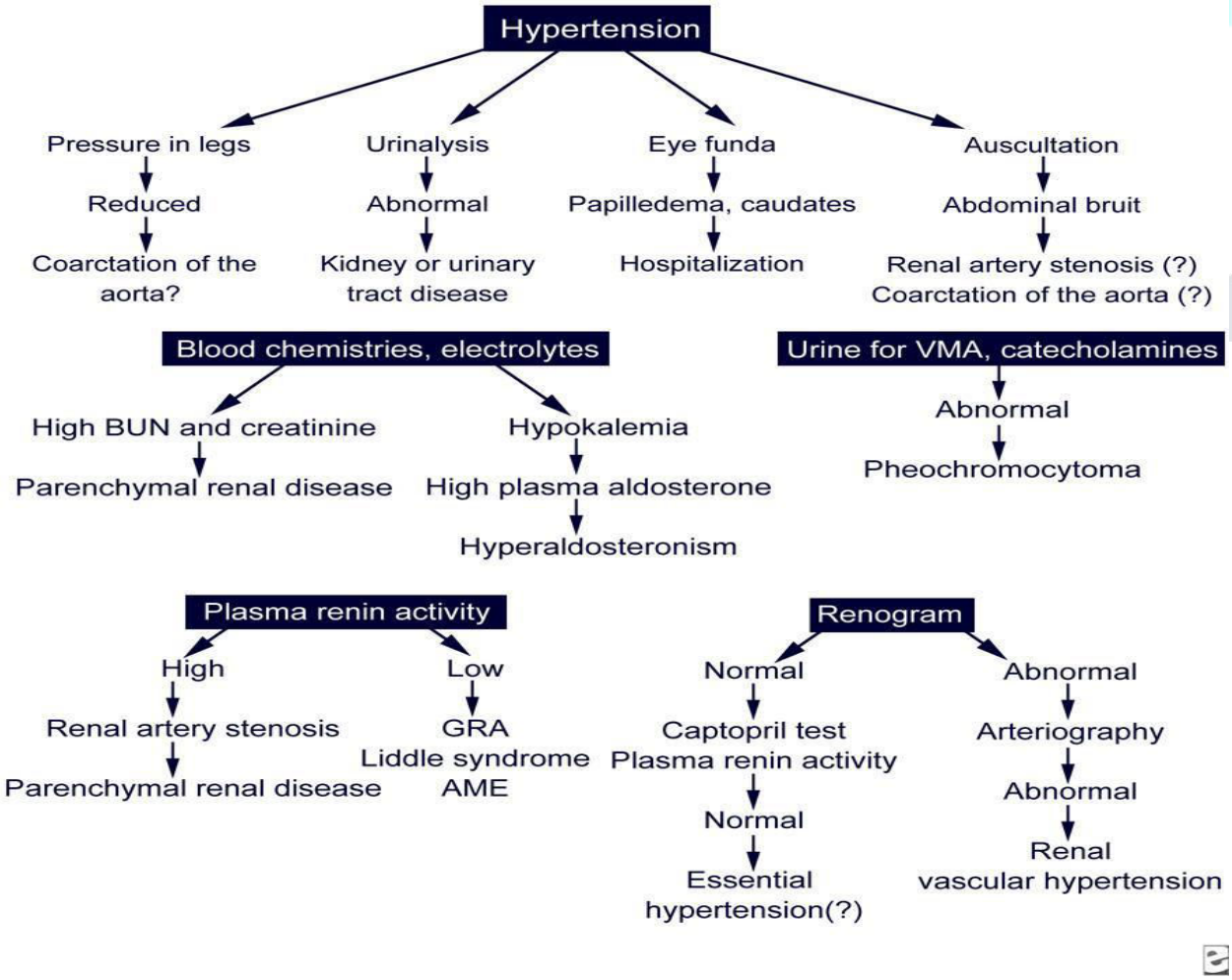


Table 445-5 Clinical Evaluation of Confirmed Hypertension

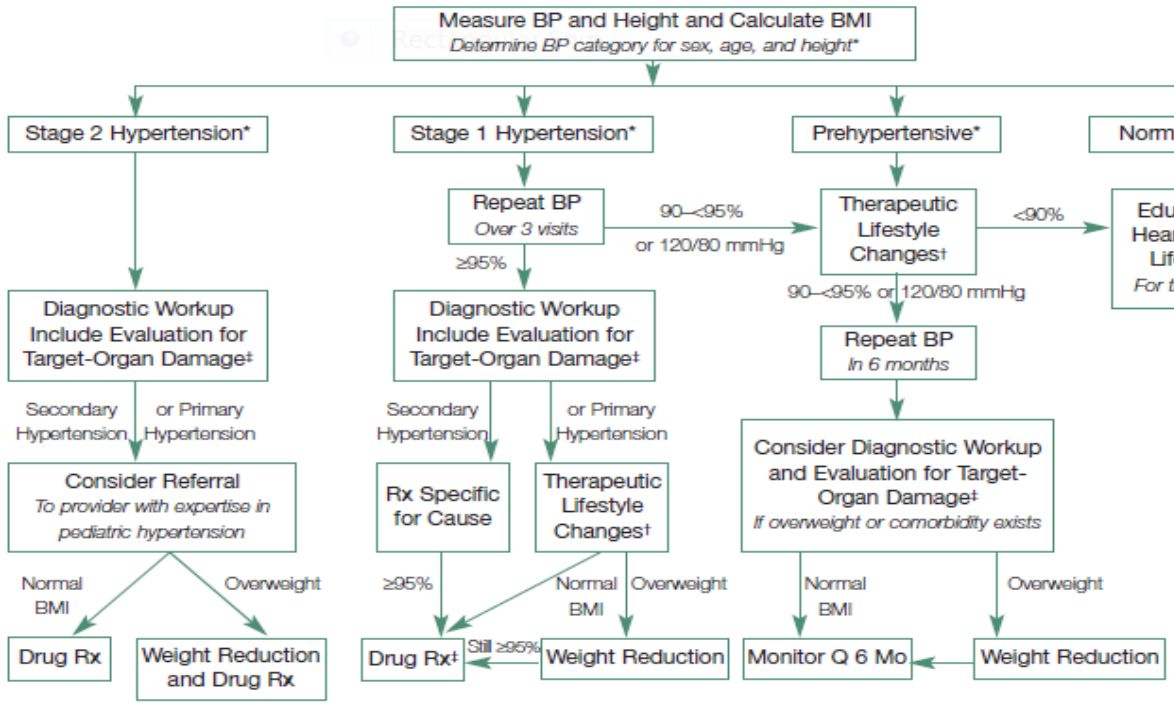
STUDY OR PROCEDURE	PURPOSE	TARGET POPULATION
EVALUATION FOR IDENTIFIABLE CAUSES		
History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination	History and physical examination help focus subsequent evaluation	All children with persistent BP ≥95th percentile
Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture	R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states	All children with persistent BP ≥95th percentile
Complete blood count	R/O anemia, consistent with chronic renal disease	All children with persistent BP ≥95th percentile
Renal ultrasound	R/O renal scar, congenital anomaly, or disparate renal size	All children with persistent BP ≥95th percentile
EVALUATION FOR COMORBIDITY		
Fasting lipid panel, fasting glucose	Identify hyperlipidemia, identify metabolic abnormalities	Overweight patients with BP at 90th-94th percentile; all patients with BP ≥95th percentile; family history of hypertension or cardiovascular disease; child with chronic renal disease
Drug screen	Identify substances that might cause hypertension	History suggestive of possible contribution by substances or drugs.
Polysomnography	Identify sleep disorder in association with hypertension	History of loud, frequent snoring
EVALUATION FOR TARGET-ORGAN DAMAGE		
Echocardiogram	Identify left ventricular hypertrophy and other indications of cardiac involvement	Patients with comorbid risk factors* and BP 90th-94th percentile; all patients with BP ≥95th percentile
Retinal exam	Identify retinal vascular changes	Patients with comorbid risk factors and BP 90th-94th percentile; all patients with BP ≥95th percentile
ADDITIONAL EVALUATION AS INDICATED		
Ambulatory blood pressure monitoring	Identify white coat hypertension, abnormal diurnal BP pattern, BP load	Patients in whom white coat hypertension is suspected, and when other information on BP pattern is needed
Plasma renin determination	Identify low renin, suggesting mineralocorticoid-related disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension Positive family history of severe hypertension
Renovascular imaging Isotopic scintigraphy (renal scan) Magnetic resonance angiography Duplex Doppler flow studies 3-Dimensional CT Arteriography: digital subtraction arteriography or classic	Identify renovascular disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine steroid levels	Identify steroid-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine catecholamines	Identify catecholamine-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension

- **Management of hypertension**

  - **Goals of management :**

1. To reduce blood pressure below the 95th percentile for age, height and gender.
2. To reduce blood pressure below the 90 th percentile for age, height and gender if CHD , CKD , DM , target organs damage.

Management Algorithm



- **Non pharmacologic measures**

Intervention focus on the risk factors:

1- Weight reduction may result in a 5–10 mm Hg reduction in systolic pressure.
2- A reduction in sodium intake (reductions in BP, in the range of 1–3 mmHg)
3- program of aerobic exercise in patients with mild essential hypertension.
4- Adolescents should be counseled about the adverse effects of tobacco and alcohol on blood pressure.

- **When the patient is unable to cooperate with the non-pharmacologic approach or the reduction in blood pressure is insufficient, antihypertensive agents should be prescribed**

- **Pharmacologic measures**

Indications :

1- Symptomatic hypertension.
2- Secondary hypertension.
3- Hypertensive target-organ damage (LVH, retinopathy, proteinuria).
4- Diabetes (type 1 and 2).
5- Hypertension that persists despite non pharmacologic measures.

- Pharmacotherapy should follow a step-up plan.
- Introducing one medication at a time at the lowest dose, then increasing the dose until therapeutic effects are seen, side effects are seen, or the maximal dose is reached.
- If BP is not controlled, a drug from another class should be added.
- If no control with 2 drugs, reconsider the possibility of 2ry hypertension before adding a third drug.

- **Options :**

- CCB are most frequentely chosen first line .
- Beta blockers , diuretics , ACEI can be also considered as first line management
- Alpha blockers also can be used

- **<u>CCB</u>**

- Amlodipine .. Felodipine.
- They decrease systemic vascular resistence
- Side effects :
  1- edema
  2- flushing .. Headache
  3- reflex tachycardia
  4- hypotension

- **<u>ACE inhibitors</u>**

- *Prefered for children with :
  1- diabetes and microalbuminuria
  2- proteinuric renal disease
  3- high-renin hypertension 2ry to renovascular or renal parenchymal disease
  4- patients with high-renin essential hypertension.

- *Contraindications :
  1- bilateral renal vascular diseases
  2- single kideny
  3- renal perfusion is maintained by high level of Angiotensin 2

* You have to check serum potassium and creatinine before giving and periodically to monitor for hyperkalemia and azotemia..

- Side effects :
  1- cough … use ARBs
  2- Angioedema
  3- hyperkalemia
  4- hypotension

- Cough and angioedema are reportedly less common with newer members of this class than with captopril.

- Benazepril, enalapril, and lisinopril ,captopril can prepared as suspension.
- FDA approval for ACE inhibitors with pediatric labeling is limited to children ≥6 years of age and to children with creatinine clearance ≥30 ml/min/1.73m2.

- **Beta-blockers**

- Preferred : for children with hypertension and migraine headache
- Contraindications for beta B :
  1- Asthma , reactive airway disease
  2- Heart faliure
  3- insuline dependant DM

- **Diuretics**

1. All patients treated with diuretics should have electrolytes monitoring shortly after initiating therapy and periodically thereafter.
2. Useful as add-on therapy in patients being treated with drugs from other drug classes.

- Furosemide is labeled only for treatment of edema but may be useful as add-on therapy in children with resistant hypertension, particularly in children with renal disease
- Potassium-sparing diuretics (spironolactone, triamterene, amiloride) may cause severe hyperkalemia, especially if given with ACE inhibitor or ARB.
- Chlorthalidone may precipitate azotemia in patients with renal diseases and should be used with caution in those with severe renal impairment.

- **α-Adrenergic blockers**
  (phentolamine, phenoxybenzamine)

- Used for neural crest tumors (high circulating levels of catecholamines) + ß-blockers to control the HR
- or use an agent with dual blocking action labetalol ..Can reduce systemic vascular resistence with little effect on stroke volume)

- **Medications**

drug	Dosage Range	Route	duration	S.E
Labetalol (a and ß Blockade)	0.25_ 2.0mg/kg/hr 1–3mg/kg/24 hr	IV cont PO	6-12 hr	dizziness, bronchospasm
Propranolol (ß-Receptor Blockade)	0.01–0.1 mg/kg/dose 0.5–6.0 mg/kg/24 hr, max 60 mg/24 hr	IV slow push PO	6-8 hr	Bronchospasm, bradycardia, vivid dreams
Hydrochlor-othiazide	1–2 mg/kg/24 max of100 mg/24 hr	PO	12-24 hr	Hypokalemia, hyperuricemia, hypercalcemia

Drug	Dosage range	Route	Duration	S.E
Furosemide	1–2 mg/kg/dose up to 6 mg/kg/24 hr	IV PO	4–6 hr 6–12 hr	Hypokalemia, alkalosis
Enalapril (ACE-I)	Children: 0.2–1 mg/kg/24 hr Adolescents: 2.5–5 mg/24 hr up to 40 mg/24 hr	PO	12–24 hr	Hypotension
Nitroprusside Vasodilator	0.5–8.0 µg/kg/min	IV	With infusion	Thiocyanate production, rarely hypothyroidism
Nifedipine CCB	0.25–0.5 mg/kg/dose max of 10 mg/dose	PO SL	4-6 hr	Facial flushing, tachycardia

- **Management of hypertensive crisis**

1- prompt hospitalization
2- Use IV line for giving anti HTN
3- select an agent with a rapid and predictable onset of action and to monitor blood pressure carefully as it is being reduced.

- **Choices :**

1- IV Labetalol
2- IV Nitroprusside
3- sublingual Nifidipin
4- Intravenous hydralazine and diazoxide are alternative but may not provide the desired gradual reduction.

✓ **NOTE** : Too rapid reduction in blood pressure may interfere with adequate organ perfusion, a stepwise reduction in pressure reduced by about 1/3rd of the total planned reduction during the 1st 6 hr and the remaining amount over the following 48–72 hr.
should be planned.

- **Options for secondary HTN**

1- 1- Interventional cardiac catheterization procedures can be used to treat coarctation of the aorta.

2- Balloon dilation +/- stent placement, can be used for treatment of recurrent coarctation.
3- n children with renal artery stenosis ..percutaneous balloon angioplasty
4- **Surgery may be required for children with:**

- severe renal vascular hypertension
- renal segmental hypoplasia
- Wilms tumor
- coarctation of the aorta
- pheochromocytoma.

Hemolytic uremic syndrome (HUS)

- **HUS** is the most common cause of acute kidney injury AKI in the pediatric population.
- It is characterized by the triad of:
  1- Microangiopathic hemolytic anemia (MAHA)
  2- Thrombocytopenia
  3- Renal insufficiency
- The clinical course of hemolytic-uremic syndrome can vary from subclinical to life threatening .

- **Epidemiology**

- Was first defined in the literature in 1955 .
- Incidence increases during summer and early fall .

- **International** :
  It occurs worldwide but has a higher incidence in South Africa , Holland and Argentina . The largest outbreak until now occurred in **Germany** in 2011 .

- **Race** : Occurs in all races ; however it is very rare in black .

- **Sex** :Male : female 1:1 , but it is more severe in females .

- **Age :**
  - ✓ D+ HUS occur in children aged 7 months to 6 years .
  - ✓ D-HUS has No age predilection .
  - ✓ Genetically mediated forms may present as early as birth or the neonatal period

- **Mortality/Morbidity :**
  - ✓ Mortality rates have decreased progressively from near universal fatality in 1955 to only 3-5% during the 1990s.
  - ✓ Patients with hereditary HUS have a worse prognosis.
  - ✓ The vast majority of patients with autosomal dominant or recessive forms of the disease progress to ESRD.

- **Etiology**

- Hemolytic uremic syndrome (HUS) is a condition caused by the abnormal destruction of red blood cells. The damaged red blood cells clog the filtering system in the kidneys, which can lead to life-threatening kidney failure.
- HUS usually develops in children after 5-10 days of **diarrhea** (often bloody) caused by infection with certain strains of **Escherichia coli** (E. coli) bacteria. Adults also can develop HUS due to E. coli or other types of infection, certain medications, or pregnancy.
- The most common type of HUS is associated with a prodromal diarrheal illness (**D+HUS).** Contamination of meat, fruit, vegetables, or water with verotoxin (VT)-producing Escherichia coli (most commonly **E.coli O157:H7)** is responsible for many outbreaks.

- VT may be produced by other E. coli strains as well as other bacteria such as Shigella. VT causes hemorrhagic enterocolitis of variable severity and results in HUS in **5-15%** of affected children.

• **D+ HUS and EHEC**

- EHEC (bloody diarrhea with gastroenteritits symptoms & manifestations) colonise cattle .
- Transmission route was highest in:
    1- 1-Swimming outbreaks
    2- 2-Person-to-person (Daycare centers)
    3- Animal contact
    4- Food-borne (contaminated ground beef) and drinking water–related outbreaks.

• **Other causes of hemolytic-uremic syndrome include infection by the following:**
    - Shigella dysenteriae
    - Salmonella typhi
    - Campylobacter jejuni
    - Yersinia species
    - Pseudomonas species
    - Bacteroides species
    - Entamoeba histolytica
    - Aeromonas hydrophilia

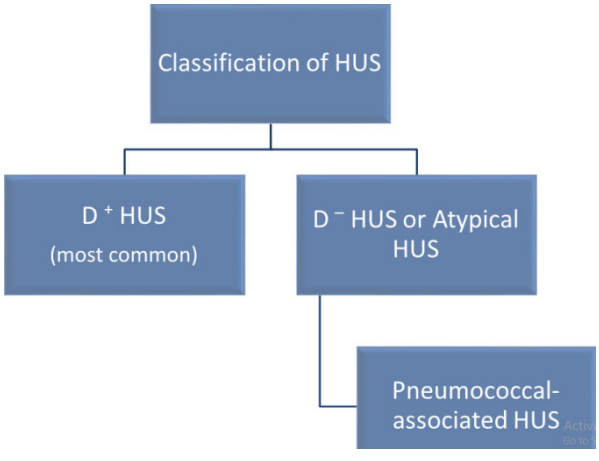
• HUS presenting without a prodrome of diarrhea (**atypical HUS)** may occur at any age. The clinical course is usually **more severe** than that of D+HUS.

Atypical HUS can be secondary to infection (Streptococcus pneumonia, HIV), genetic and acquired defects in complement regulation, medications, malignancy, SLE , and pregnancy.

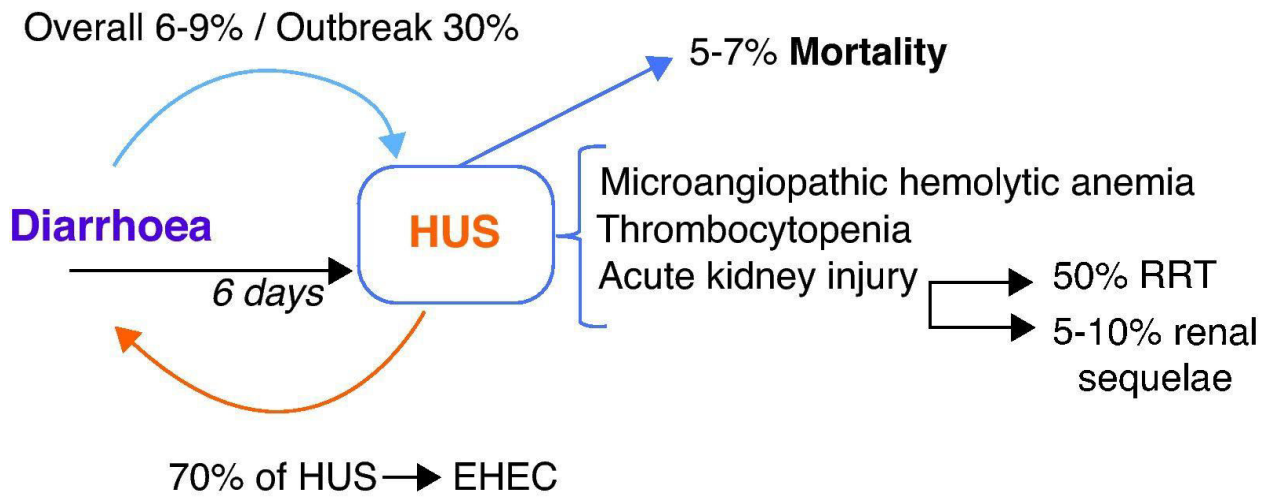
• **Classification**

- **STEC-HUS** (Shiga toxin-producing Escherichia coli) **:** is used to describe HUS mediated by Shiga toxin (Stx)–producing Escherichia coli. This is also called **classic**, **typical**, **Stx**, **diarrhea-positive**, or **D $^{+}$ HUS**.

- **Atypical HUS (aHUS) :** is used to describe HUS not mediated by Shiga toxin. This is also called **diarrhea-negative**, **non–diarrhea-associated**, or **D $^{-}$ HUS** . This disease is usually mediated by <u>abnormalities of the complement system</u> or other heritable factors.
    ☒ **Pneumococcal-associated HUS :** is a subtype of **atypical** HUS , mediated by <u>neuraminidase</u> in the presence of infection with **Streptococcus pneumoniae**.
    This is also called **neuraminidase-associated HUS** .



- Classic D+HUS begins with enterocolitis, often with bloody stools, followed **in 7 to 10 days** by weakness, lethargy, and oliguria/anuria.



- Children without evidence of a diarrheal prodrome may have a similar microangiopathic syndrome, identified as **thrombotic thrombocytopenic purpura (TTP).**

	HUS	TTP
Clinical features	1- thrombocytopenia 2- MAHA 3- Renal involvement (30% have CNS involvement and fever)	1- thrombocytopenia 2- MAHA 3. Mild renal involvement 4. Fever 5. CNS involvement (60% may not have the pentad)
Age	Children	Adults
Mechanisms	Diarrhea+: Shiga toxin Diarrhea -: Alternative complement disorders	ADAMTS-13 abnormalities

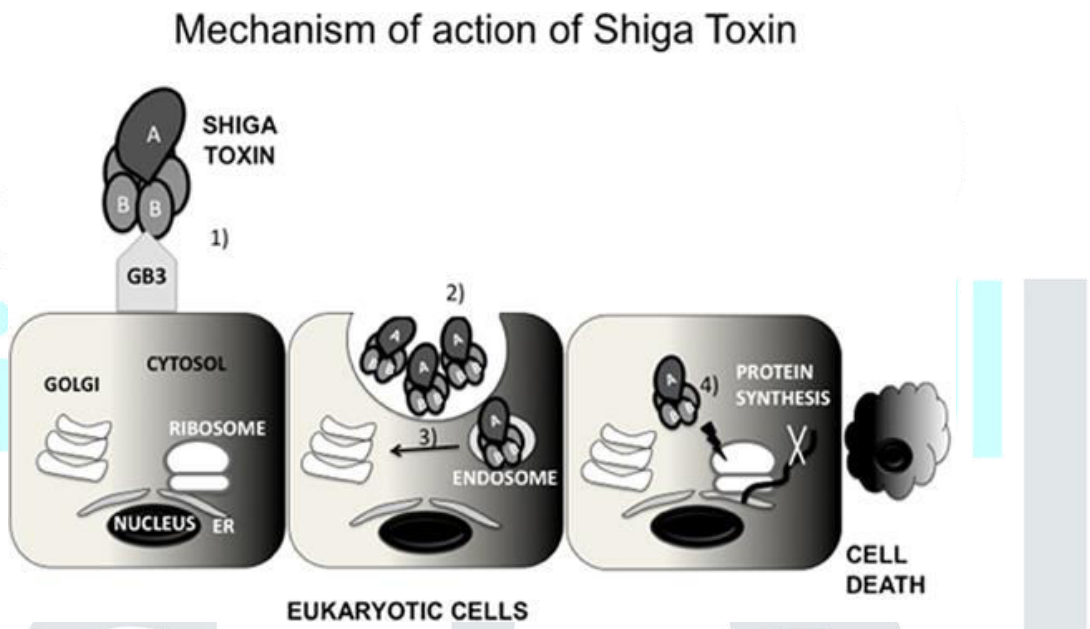
- Children with **TTP** typically have predominant CNS symptoms but may also have significant renal disease. Recurrent episodes are common. Because CNS involvement is also seen in HUS, TTP can be difficult to distinguish from HUS in some cases.
- The traditional classification describes patients with predominantly renal disease as having HUS , and patients with predominantly CNS disease as having TTP. However, HUS can include severe neurologic impairment, and TTP can involve severe renal failure.
- Deficiencies of **ADAMTS13**, a von Willebrand factor-cleaving protease, have been identified in children affected with TTP.

- Patients with very low ADAMTS13 activity (generally less than 10%) are considered to have TTP, while higher levels of activity point to a diagnosis of HUS.

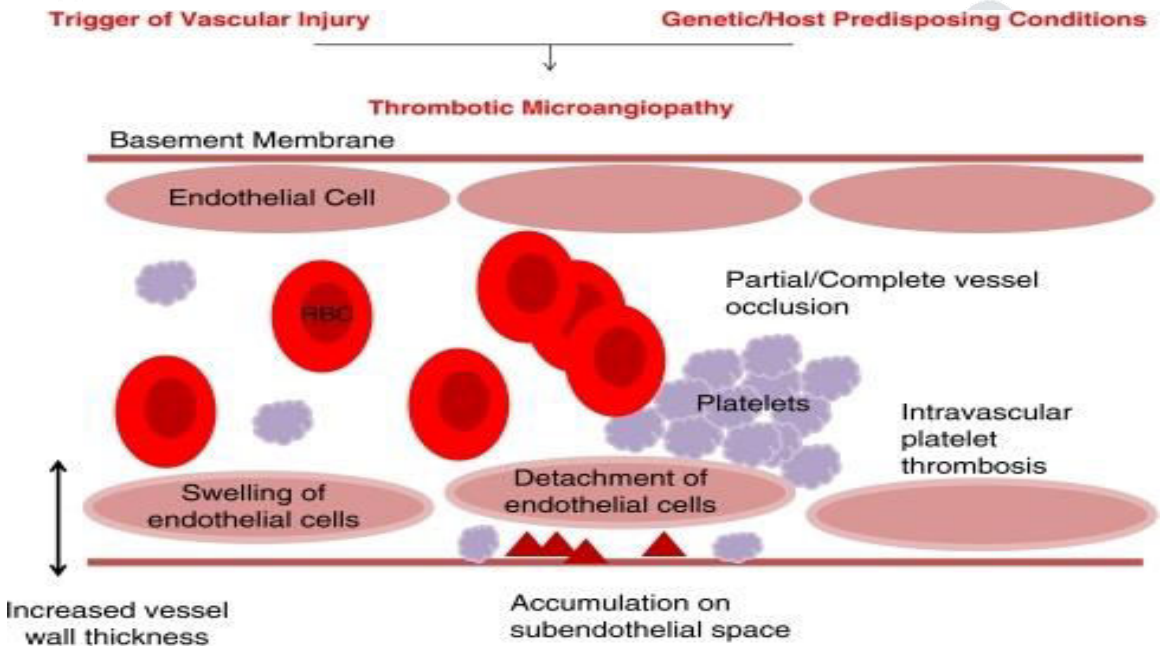
- **Pathophysiology**
- **STEC-HUS**

- STEC-HUS is <u>usually preceded</u> by a colitis caused by (STEC).
- Inflammation of the colon facilitates systemic absorption of the Stx and lipopolysaccharide from the GI tract .
- These toxins bind to globo-tri-aosylceramide (Gb3), a glycolipid receptor molecule on the surface of capillary endothelial cells in the gut, kidney, and, occasionally other organs. which leads to damage of endothelial cells.

- **Typical HUS:**



- **Endothelial injury and Thrombotic microangiopathy:**



- Damaged endothelial cells of the glomerular capillaries release vasoactive and platelet-aggregating substances. The endothelial cells swell, and fibrin is deposited on the injured vessel walls.

- Swelling and microthrombi formation within the glomerular capillaries produce a localized intravascular coagulopathy. The glomerular filtration rate is reduced, and renal insufficiency ensues.

- Erythrocytes are damaged and fragmented as they traverse the narrowed glomerular capillaries. This leads to the characteristic microangiopathic hemolytic anemia

- Differential expression of Gb3 on glomerular capillaries compared with other endothelial cells may explain the predominance of renal injury.

- Thrombocytopenia is believed to result from a combination of
    1. platelet destruction,
    2. increased consumption,
    3. sequestration in the liver and spleen,
    4. and intrarenal aggregation

- **Clinical Triad of HUS**

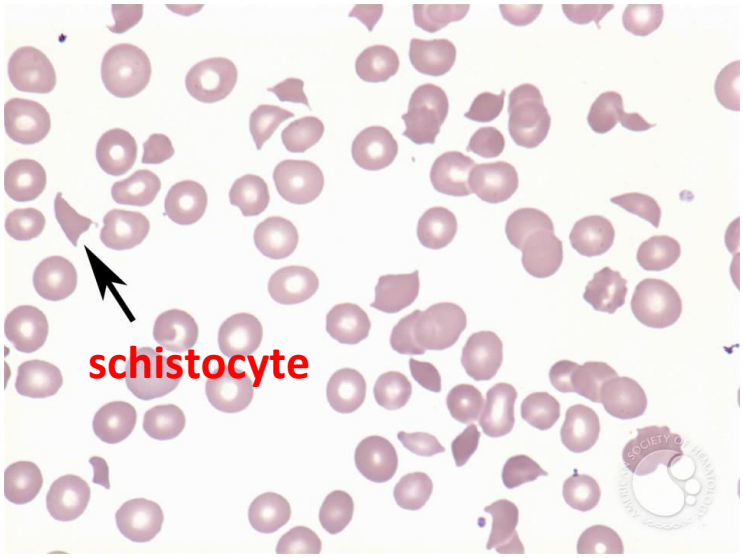
1. Microangiopathic hemolytic anemia:

- Hemoglobin levels usually less than 8 g/dL
- Negative Coombs' tests
- Peripheral blood smear with a large number of **schistocytes** (up to 10 percent of red cells) .

✓ Additional findings of hemolysis include elevation of the serum indirect bilirubin concentration and reduction in the serum haptoglobin concentration .The serum lactate dehydrogenase (LDH) level is typically very high.

✓ Although hemolysis may occur over a several-week period, there is no correlation between the severity of anemia and the severity of renal disease.

- Microangiopathic hemolytic anemia:



2. Thrombocytopenia:

- Thrombocytopenia is characterized by a platelet count below 140,000/mm3 and usually about 40,000/mm3.
- Despite this, there is usually no purpura or active bleeding.

3. Acute renal injury:

- The severity of renal involvement ranges from hematuria and proteinuria to severe renal failure and oligoanuria.
- Severe renal failure occurs in one-half of cases.
- **Hypertension** is common, Most patients have microscopic hematuria on urinalysis, although macroscopic hematuria may be observed.
- Red blood cell casts are occasionally seen, but are not a typical feature.

- **Clinical manifestations**

•**Central nervous system** – Manifestations of central nervous system (CNS) involvement, which are seen in up to 20 % of children with **Stx HUS**, include seizures, coma, stroke, hemiparesis, and cortical blindness.

In patients with severe neurologic findings, brain MRI reveals bilateral hypersignal on T2-weighted and hyposignal on T1-weighted images in the basal ganglia, thalami, and brainstem. Severe CNS involvement is associated with increased mortality.

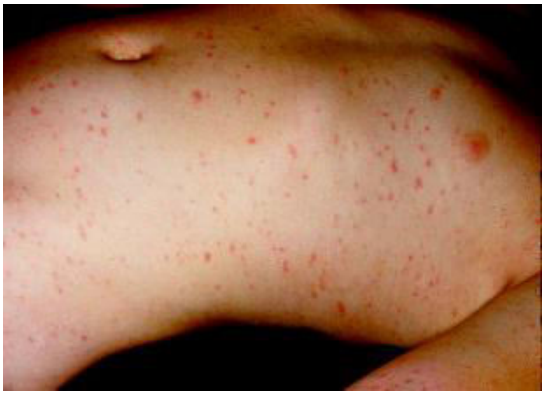
•**Gastrointestinal tract** – Any area from the esophagus to the perianal area can be involved. The more serious manifestations include severe hemorrhagic colitis, bowel necrosis and perforation, rectal prolapse, peritonitis, and intussusception.

• **Cardiac dysfunction** – Cardiac dysfunction can be due to cardiac ischemia detected by elevated levels of troponin 1 and fluid overload.

• **Pancreas** – During the acute phase, less than 10 % of patients develop glucose intolerance. Transient diabetes mellitus may occur and rarely permanent diabetes mellitus, which may develop years later.

• **Liver** – Hepatomegaly and/or increased serum transaminases are frequent findings.

- Physical examination reveals irritability, pallor, and petechiae. **Dehydration** is often present; however some children have volume overload. **Hypertension** may be due to volume overload and/or renal injury.



- **Evaluation and diagnosis**

- A patient with a recent history of diarrhea (**possibly bloody**) who presents with S&S of a multisystem disorder requires a quick and accurate assessment for the possible development of (HUS). As an example, decreasing urine volume in an adequately hydrated child with diarrhea should prompt the consideration of new-onset renal injury, particularly due to HUS.

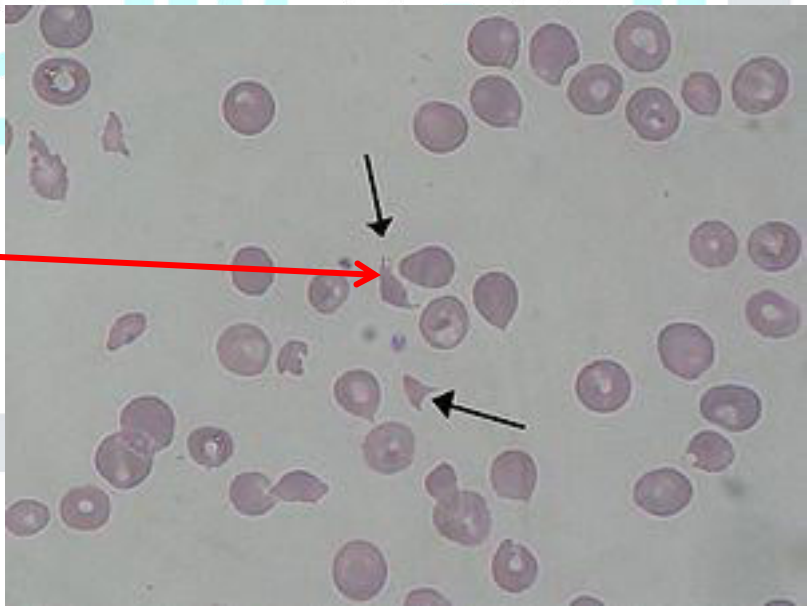
- The diagnosis of (Stx) HUS in children is generally made on clinical grounds from the characteristic clinical and laboratory findings a **prodrome of diarrhea,** followed by abrupt onset of the characteristic triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury.

- Although laboratory diagnosis of enterohemorrhagic E. coli infection can be made by stool culture, the bacteria are only present in the stools for a few days and, even if present, may not be detected by culture.

- Other evidence of E. coli infection include detection of **Shiga-toxin genes** in stools by (PCR) or serum IgM antibodies against lipopolysaccharide of major enterohemorrhagic E. Coli

- **Diagnostic studies**

- Peripheral blood smear reveals evidence of microangiopathic hemolysis. Coombs test is **negative**. The diarrhea and presence of toxin-producing E. coli may have resolved by the time HUS is diagnosed.



- Common Laboratory Findings with Hemolytic Uremic Syndrome:

EVIDENCE OF MICROANGIOPATHIC HEMOLYTIC ANEMIA :	EVIDENCE OF RENAL INJURY :
• Anemia • Thrombocytopenia • Presence of schistocytes, helmet cells, and burr cells on peripheral blood smear • Increased LDH • Decreased haptoglobin • Increased indirect bilirubin • Increased AST • Elevated reticulocyte count	• Elevated creatinine • Presence of hematuria, proteinuria, pyuria, casts on urinalysis
	OTHER POTENTIAL FINDINGS :
	• Leukocytosis • Positive stool culture for E. coli O157:H7 • Positive stool test for shiga-toxin • Elevated amylase/lipase

Renal biopsy, which is rarely performed, may be helpful in selected patients in whom the diagnosis is uncertain and thrombocytopenia is not limiting.

- The characteristic prodrome of diarrhea is absent in some affected children. In this setting, the presence of the defining triad in an age appropriate child should prompt consideration of infection of other organs, particularly the urinary tract, with a Shiga toxin-producing organism. The diagnosis may be confirmed with serologic testing or a positive microbial culture

- **Differential diagnosis :**
    1. Enteric infections
    2. Henoch-Schönlein purpura.
    3. DIC

- Severe abdominal pain, frankly bloody diarrhea, fever, and leukocytosis occur in other enteric infections (such as Salmonella, Campylobacter, Yersinia, amebiasis, and Clostridium difficile), and with Henoch-Schönlein purpura.

- With severe diarrhea, elevations in the serum creatinine concentration and BUN are typically due to volume depletion, not intrinsic renal disease. Thus, the combination of severe diarrhea and renal insufficiency due to volume depletion may be confused with that due to HUS.

- The distinction between HUS and **DIC** is more difficult, and is based upon the history and laboratory studies. DIC is associated with intravascular activation of the coagulation cascade, leading to intravascular deposition of fibrin thrombi, the consumption of all of the components of this cascade, and microangiopathic hemolytic anemia.

- As a result, patients with DIC typically have thrombocytopenia, low circulating levels of fibrinogen and factors V and VIII, and prolongation of the prothrombin and partial thromboplastin times (PT and aPTT, respectively). And positive FDP and D Dimer

- In comparison, patients with Shiga toxin (Stx) HUS have **isolated platelet consumption** due to endothelial injury.

- The net effect is thrombocytopenia; increased turnover of platelets, but not fibrin; and usually normal levels of the coagulation components, and little or no prolongation of the PT or aPTT.

- **Atypical HUS causes**

  NStx HUS is defined by the characteristic triad of HUS (microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury), **but without a diarrheal prodrome.**

- As previously mentioned, some cases of Shiga toxin associated HUS may not present with colitis and diarrhea. Unlike Stx disease, NStx HUS is more likely to recur, have a severe clinical course (particularly renal insufficiency and hypertension), and be associated with a **positive family history**.

- Uncommon
- Up to 50% or more may have mutations in genes of complement components and regulators
- Poor prognosis
- Treatment options depending on the mutation
- Early intervention crucial
- Implications for recurrence post transplantation
- Atypical HUS

- **When to consider Atypical HUS ?**
  - Non-bloody diarrhoea
  - Known family history of HUS
  - Children under 3 months old
  - Relapsing course

- **Atypical HUS causes**

1- Infection induced Atypical HUS:

a. Neuraminidase-producing S.pneumonia
b. HIV

2- Genetics:

a. ADAMTS 13 deficiency
b. B-Complement Abnormalities
c. Vit B12 metabolisim defects
d. Familial autosomal dominant of undefined etiology
e. Familial autosomal recessive of undefined etiology

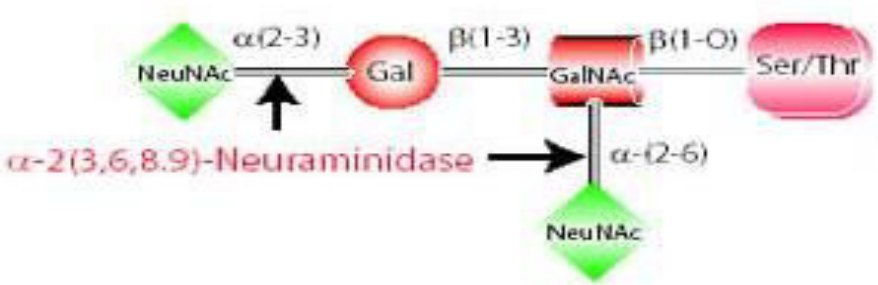
3- Drug induced :

•Among transplant patients treated with either cyclosporine or tacrolimus . It usually occurs during the first few months post-transplantation, a time when high doses of calcineurin inhibitors are being administered.

• During treatments with cytotoxic drugs, such as mitomycin C, bleomycin , or cisplatin .
•With the administration of ticlopidine and quinine , and oral contraceptives.

A- PNEUMOCOCCAL-ASSOCIATED

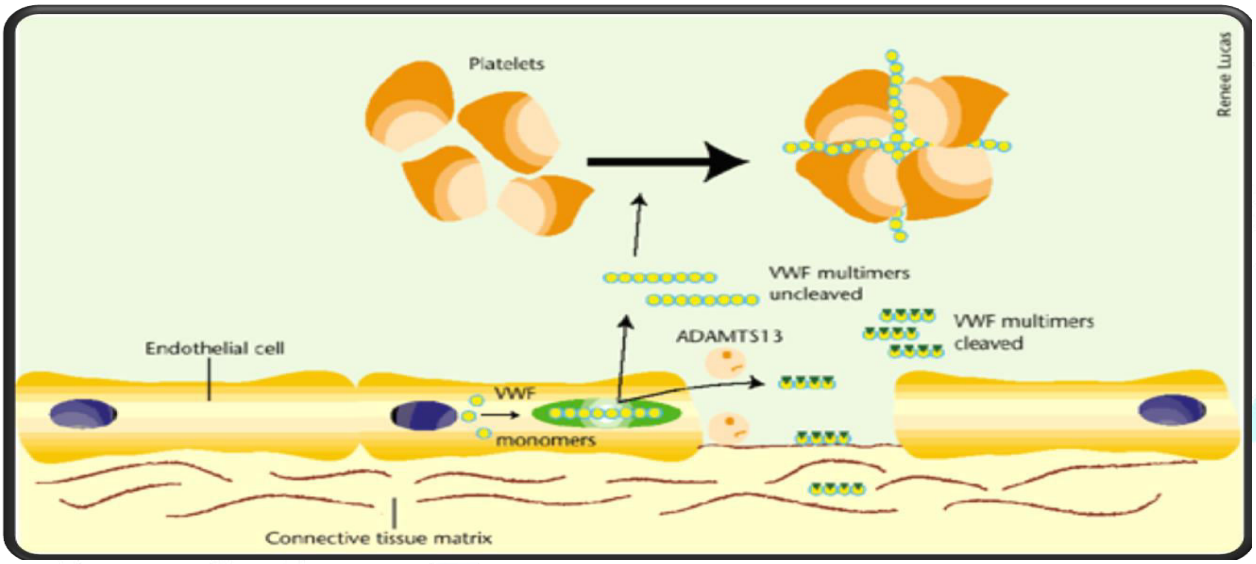
❖ pathogenesis :
- microbial neuraminidase exposes Thomsen-Friedenreich (T) antigen
- cryptic T-antigen found on erythrocytes, platelets, and glomeruli



- neuraminidase cleaves sialic acid, exposing T-antigen
- bound by “natural” anti-T IgM antibodies
- results in thrombotic microangiopathy
- HUS develops during acute infection ,typically manifesting as pneumonia with empyema.

B- Congenital deficiency of ADAMTS-13

- protease cleaves vWF multimers
- presents at birth with hemolytic anemia and thrombocytopenia
- renal involvement develops later in life
- Inhibitor auto-antibodies to ADAMTS-13 can also cause similar syndrome



C- Complement Abnormalities in HUS

1- Factor H
2- MCP (Membrane cofactor protein) CD46
3- Factor I
4- C3
5- Factor B

Endothelial cell damage
Platelet aggregation
Thrombus formation

- These mutations result in dysregulation of the complement system that leads to excessive complement activation that result in endothelial damage.

Complement Abnormality	Frequency	
Factor H	19%	Most severe 60% ESRF or death within 1 year
MCP	14%	Often have a relapsing course but with time 30% go into ESRF
Factor I	9%	50-70% ESRF at 5 years
C3	7%	
Factor B	1%	Rarest
Factor H Antibodies	11%	
Combined Mutations	8%	
None	39%	30% ESRF by 5 years

- **Renal Outcome**

Mutation	ESRF 1 year	ESRF 5 years	Recurrence Post Tx	Graft loss within 1 Year
Factor H	60%	73%	76%	81%
MCP	0%	38%	20%	1 of 2
Factor I	50%	50%	88%	100%
No Mutation	32%	32%	30%	83% - not recurrence

FACTOR H DEFICIENCY

- thought to account for 10-22% of atypical HUS cases
- reported in both familial and sporadic forms
- usually presents in infancy or early childhood, but may present in adulthood .

D- Cobalamin -C deficiency :

- disorder of vitamin B_{12} (cobalamin) metabolism
  - hyperhomocysteiemia
  - methylmalonic aciduria

- presents with atypical HUS and neurological symptoms
  - early onset seizures
  - hypotonia
  - developmental delay

- retinopathy
- macrocytic anemia
- Neutropenia

- **Management of HUS**
- **Fluid therapy**
  - Early hydration is associated with lower risk of progression to oligoanuric HUS in patients with diarrhea .
  - Monitor hydration status closely and frequently .

- **Renal function monitoring**
  - Renal function may rapidly decline, →monitor electrolytes frequently .
  - Use K-free fluids until renal function is stabilized .
  - Once fluid deficit have been replaced, restrict fluids to insensible loss plus actual output replacement .

- **Management of ARF**

- Approximately 50 % of D+ HUS require a period of dialysis .
- Consider early dialysis if pt develops :
  - fluid overload
  - Hyperkalemia
  - Acidosis
  - Hypernatremia
  - Olig oanuria resistant to diuretics .

Dialysis does not alter the course of the disease, it only supports the patient awaiting resolution of the illness .

Duration of dialysis (5-7 days) the number varies

- **Management of hematological abnormalities**

- PRBC's for symptomatic anemia.
- Maintaining a relative anemic status keeps the blood less viscous, preventing further thrombus formation .
- Transfuse plts if the count is less than 20,000 / mcl .

- **Management of HTN**

- **Calcium channel blockers** commonly used in pediatrics .
- **ACE inhibitors** are very effective but should be used with caution in individual with a decreased GFR or with hyperkalemia .

- **Nutritional support**

- Provide adequate protein and energy intake is important to prevent catabolism .
- Patients may require IV hyper alimentation due to prolonged diarrhea, colitis, abdominal pain, intestinal ileus, anorexia .
- Patients on Continuous Renal Replacement Therapy (CRRT) may require 3-4 g/kg/d of protein.

- **Antibiotics**
  - **Most pediatric nephrologists do not routinely use antibiotics in patients with D^+ HUS, based on a theoretical concern it could exacerbate the disease process**.
  - However, antibiotics should be used when indicated according to clinical judgment .

- **Special consideration for D- HUS**
  - Discontinue **offending agent** if a drug-associated cause is identified.
  - Treat **bacterial infections** (eg, *S pneumoniae*) promptly and aggressively.
  - Corticosteroid therapy may be initiated presumptively in patients with unexplained D^- HUS. (Very Controversial)
  - The role of **plasma therapy in** (P-HUS) or neuraminidase-mediated HUS remains controversial we may use albumin replacement not plasmapheresis .
  - Plasma may contain antibodies to the T antigen, which, in theory, could worsen the hemolytic process.
  - Alternately, **plasma exchange (PLEX) with plasma replacement FFP** may remove neuraminidase and decrease the amount of circulating anti–T antibody. And is important in treating other atypical D-ve HUS due to complement defects .
  - Plasma therapies are the mainstay of treatment for most forms of D^- HUS. These therapies use donor plasma products to replace the deficient or abnormal von Willebrand factor (vWF) metalloproteinase or complement factors.
  - Infusions typically consist of 20-30 mL/kg of FFP .
    - Volume overload may complicate plasma infusion, reduced renal function.
    - Hyperproteinemia, as shown by elevated serum total protein, has been reported in a patient receiving chronic plasma infusion.
  - **Most of those patients will require dialysis**

- **Management of end-stage renal disease (ESRD)**
  - Patients who develop permanent renal failure due to D^+HUS have a low risk of recurrence and can proceed to renal transplantation similar to patients with most other renal diseases.
  - Renal transplantation in patients with D^- HUS is more difficult because of the high risk of recurrence and allograft loss, with success rates of only 18-33% reported.

- **risk of recurrence**
  - The risk of recurrence varies with the complement mutation identified; such testing is essential is planning and counseling patients about transplant options:
    - ✓ Factor H mutation: 80-100% recurrence
    - ✓ Factor I mutation: 80% recurrence

- ✓ Membrane cofactor protein mutation: 10-20% recurrence
- ✓ No (known) mutation identified: 30% recurrence

- Combined liver-kidney transplant has been reported in patients with high-risk mutations such as factor H.
- Liver transplant alone is an option for patients without renal failure

- **Further Outpatient Care**
- (D^+ HUS):
  - Patients recovering from D^+ HUS should have regular follow-up until their symptoms have resolved and their hemoglobin, p
    latelet counts and renal function have returned to normal.
  - **Subclinical renal injury**, putting them at risk for future development of hypertension, proteinuria, and/or chronic renal disease.
  - Annual follow-up : urinalysis, urine albumin, serum creatinine, and fasting glucose levels .
  - Patients with idiopathic or genetically mediated D^- hemolytic-uremic syndrome usually have a persistent and relapsing course, and most require frequent and lifelong nephrology follow-up.
  - Eculizumab (Soliris) in treatment of D- HUS

- **Avoid risk factors for renal disease**

patients should be counseled on avoiding risk factors for renal disease :

- tobacco use
- obesity
- hypertension

- **Prevention**

- Avoid unpasteurized milk, juice and cider.
- Wash hands well before eating and after using the restroom and changing diapers.
- Clean utensils and food surfaces often.
- Cook meat to an internal temperature of at least 160 degrees Fahrenheit.
- Avoid taking antidiarrheal or anti-motility agents for diarrhea.
- Avoid taking antibiotics for diarrhea unless under the management
  - of a physician.
- Keep raw foods separate from ready-to-eat foods. Don't place cooked meat on plates previously contaminated by raw meat.
- Store meat below produce in the refrigerator to reduce the risk of liquids such as blood dripping on produce.
- Avoid unclean swimming areas.

- **Preventive measures for medical practitioners**

- **Avoid antibiotic treatment of patients with possible GI E coli 0157:H7 infection.**
- Use ample parenteral volume expansion with isotonic ("normal") saline in patients with suspected E coli 0157:H7 infection (eg, those with bloody diarrhea). **Early recognition is important.**

- Early and ample rehydration with isotonic saline is **associated with a lower risk of developing oligoanuric renal failure.**

- **prognosis**
- **D^+ HUS**
  - Most children (>95%) with D+ HUS who receive the appropriate treatment survive the acute phase and recover normal renal function, although some may have evidence of long-term morbidity. Recurrence is very rare.

  - **Poor prognostic indicators :**
  - Elevated WBC count at diagnosis
  - Prolonged anuria
  - Severe prodromal illness
  - Severe hemorrhagic colitis with rectal prolapse or colonic gangrene
  - Severe multisystem involvement
  - Persistent proteinuria

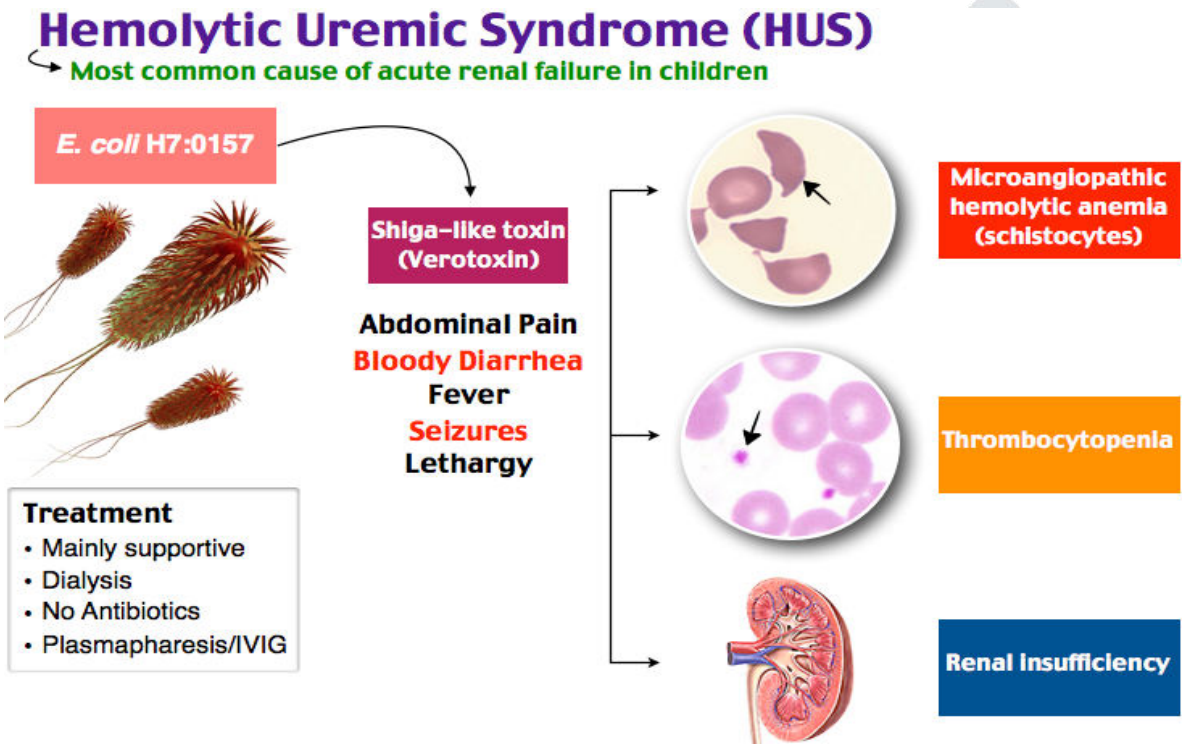
- Patients with **D^- HUS** typically have frequent relapses and a higher risk of progression to end-stage renal disease (ESRD).

- **Complications**

HUS can cause life-threatening complications, including:

- Kidney failure, which can be sudden (acute) or develop over time (chronic)
- High blood pressure
- Stroke
- Coma
- Intestinal problems, such as inflammatory colitis
- Heart problems

Summary :



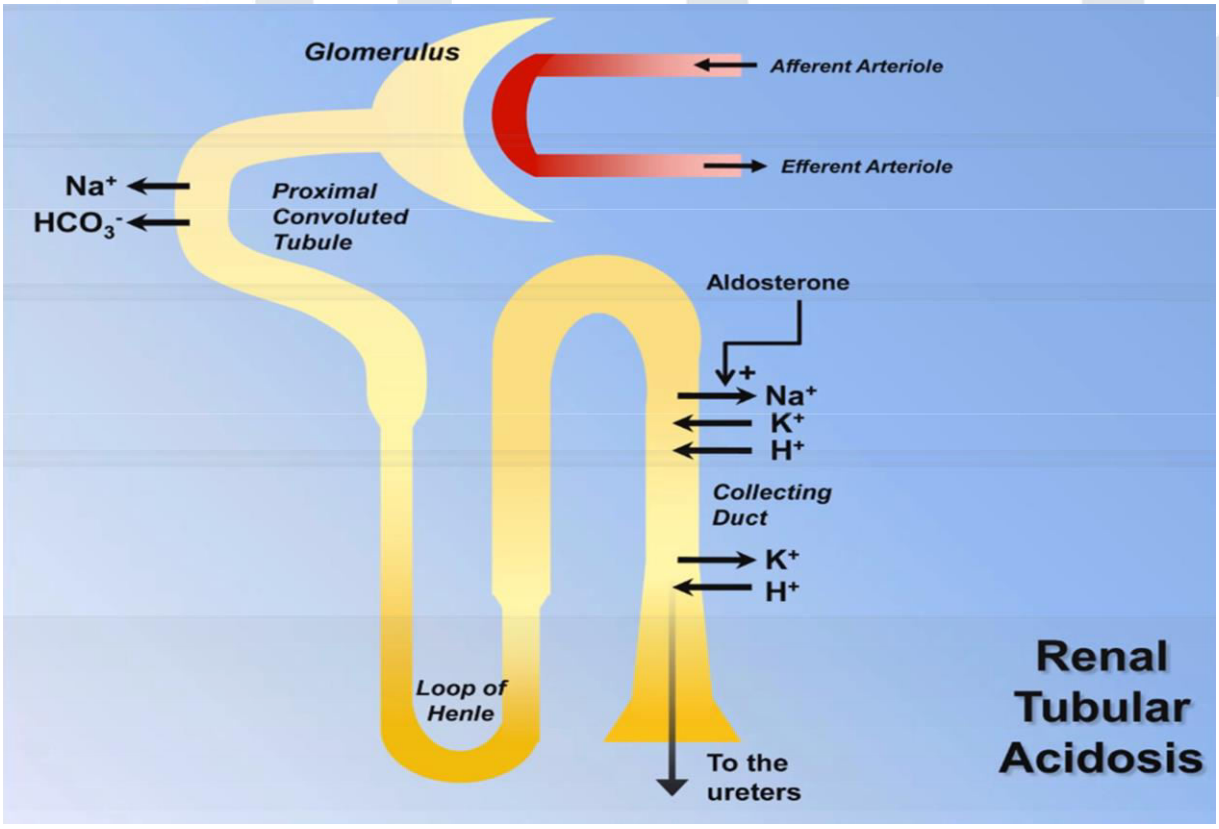
Renal tubular acidosis (RTA)

- **Is a disease state characterized by : a normal anion gap (hyperchloremic) metabolic acidosis in the setting of normal or near-normal glomerular filtration rate.**

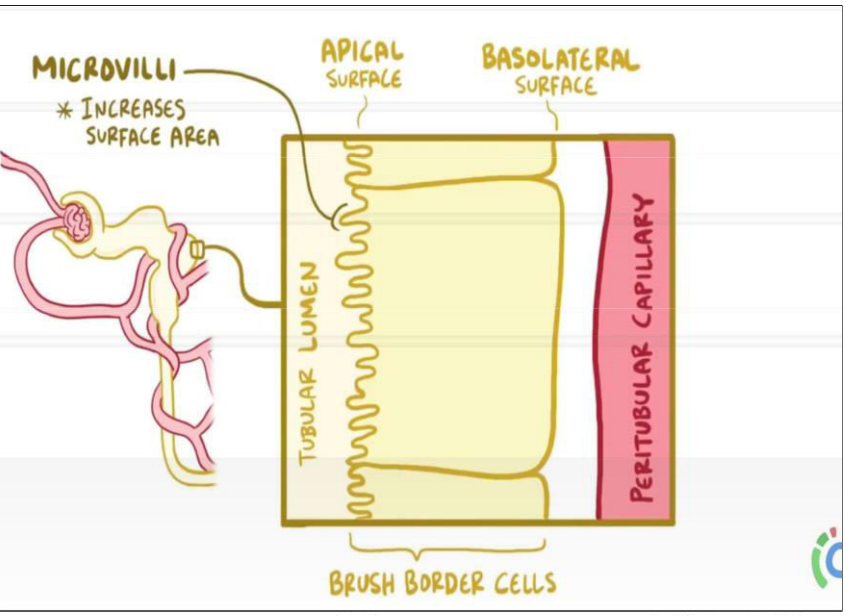
- There are 4 main types:
    1. proximal (type II) RTA
    2. classic distal (type I) RTA
    3. hyperkalemic(type IV) RTA
    4. combined proximal and distal (type III).

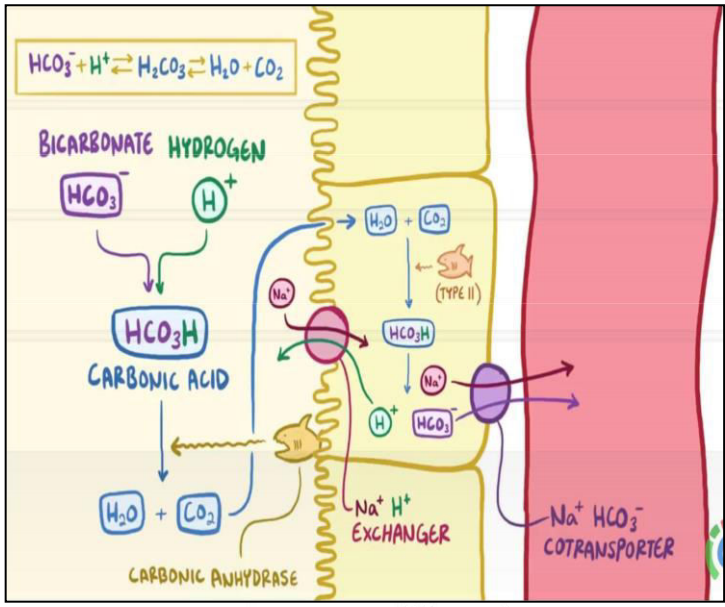
- Proximal RTA results from impaired bicarbonate reabsorption
- and distal RTA from failure to secrete acid.
  Either of these defects may be inherited and persistent from birth or acquired as is seen more commonly in clinical practice.

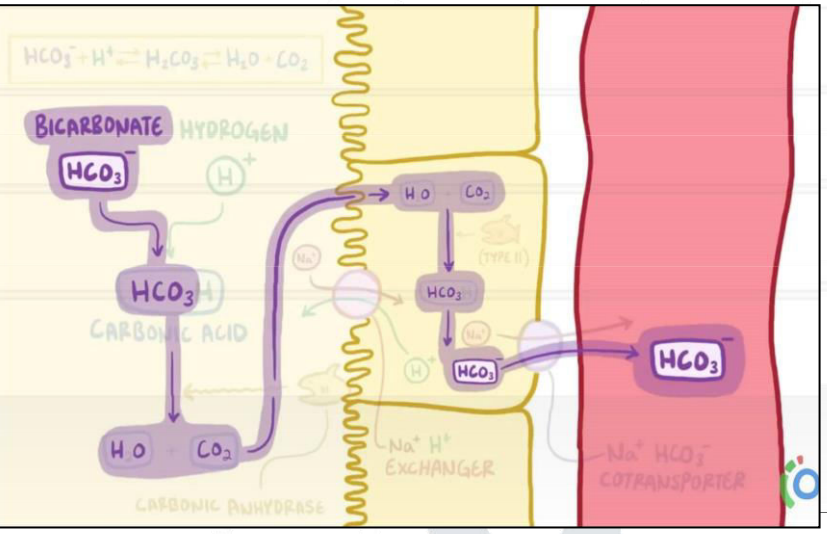
- **Normal urinary acidification**
- Kidneys contribute to acid–base balance by reabsorption of filtered bicarbonate (HCO3−) and excretion of hydrogen ion (H+) produced every day.
- Hydrogen ion secretion from tubule cells into the lumen is key in the reabsorption of HCO3 −, and the formation of titratable acid(H+ bound to buffers such as HPO42−), and ammonium ions (NH4+).
- Because loss of filtered HCO3− is equivalent to addition of H+ to the body, all filtered bicarbonate should be absorbed before dietary H+ can be excreted.
- Approximately 90% of filtered bicarbonate is absorbed in the proximal tubule, and the remaining 10% in the distal segments, mostly the thick ascending limb and outer medullary collecting tubule.

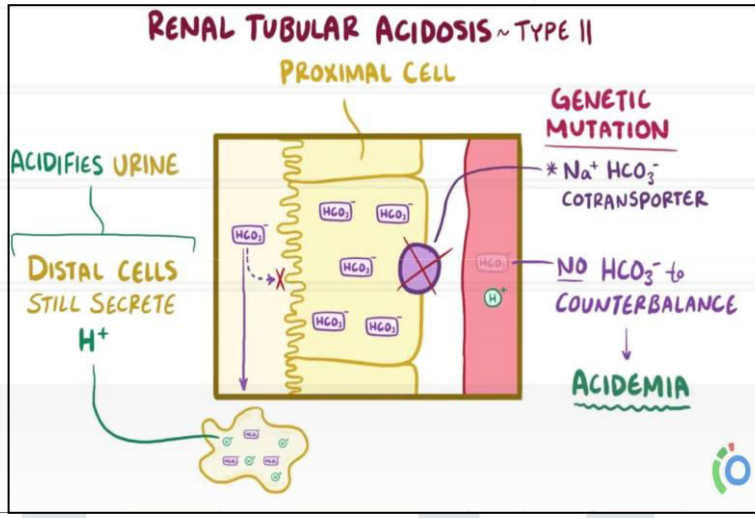


- **Type 2 (proximal RTA)**









- pathogenesis :

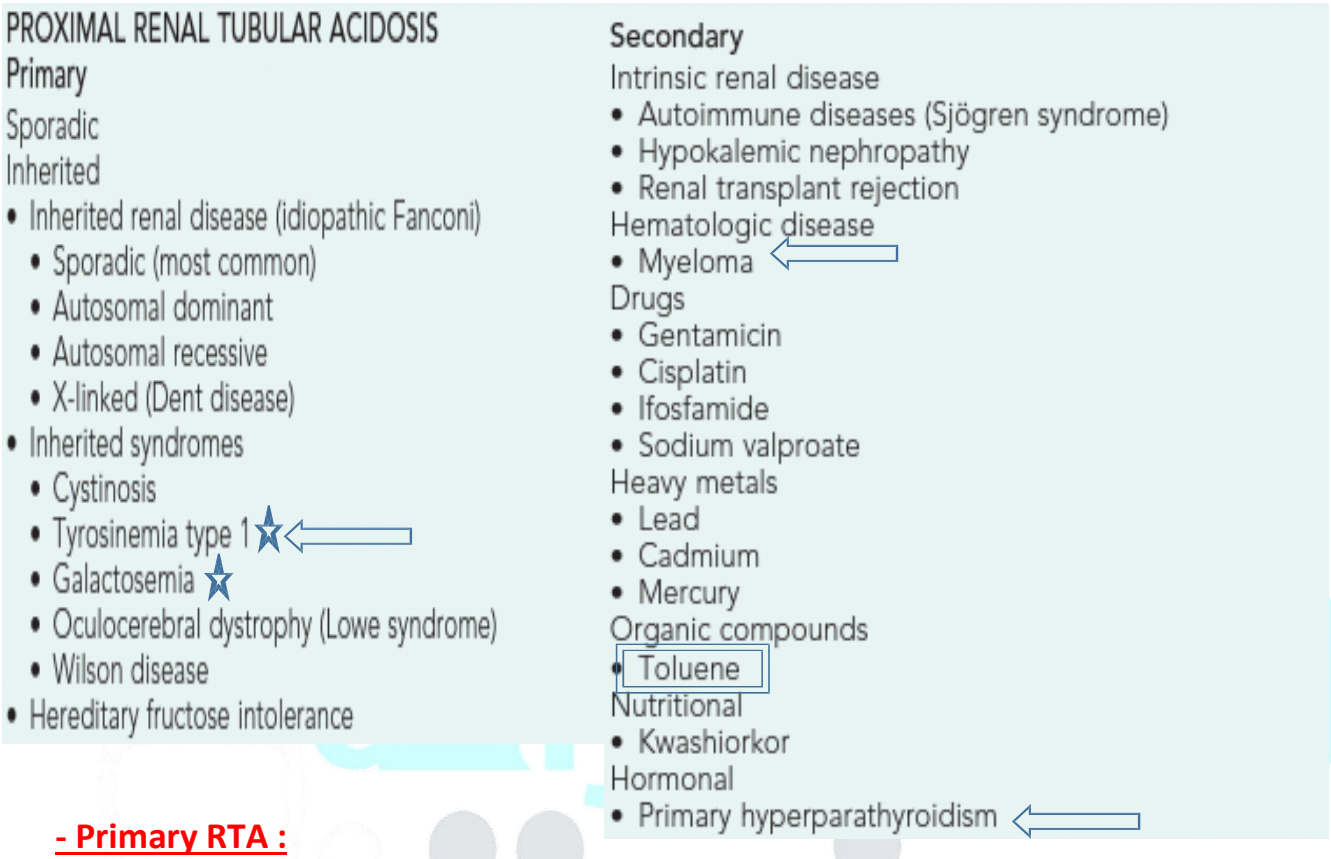
Proximal RTA can be inherited (and persistent from birth or occur as a transient phenomenon during infancy) or acquired.

- Although rare, it may be primary and isolated , or as a component of global proximal tubular dysfunction or Fanconi syndrome, which is characterized by:
  1. low-molecular-weight proteinuria
  2. glycosuria .
  3. Phosphaturia.
  4. Aminoaciduria.
  5. and proximal RTA.

- **Proximal (type II) RTA is characterized by impairment of PCT reabsorption of bicarbonate.**
- **Distal acidification mechanisms are intact.**

  The distal intercalated cells function normally, so the acidemia is less severe than dRTA and the alpha intercalated cells can produce H+ to acidify the **urine to a pH of less than 5.5**

- **In proximal RTA, the serum potassium concentration tends to be low.**
  Potassium wasting is a result of increased sodium delivery to the distal tubule promoting potassium excretion and causing secondary hyperaldosteronism.



- Primary RTA :

Transient or sporadic proximal RTA:

-Infants have a decreased capacity to bind bicarbonate without any identifiable cause or evidence of renal abnormality.

-These infants have extended ***functional immaturity*** *of* the ***proximal sodium-hydrogen exchanger*** (or antiporter), resulting in an ***age-based*** *decrease* in ***bicarbonate reabsorption*** capacity.

-Patients usually *present within* the ***first year of life*** with symptoms of *tachypnea, growth failure, recurrent vomiting,* and *feeding* difficulties

-*Resolution* of symptoms and a ***rapid*** increase in growth are seen with ***alkali therapy***, which can be discontinued after several years without recurrence of RTA and its symptoms.

Autosomal Recessive Disease

Isolated autosomal recessive pRTA is caused by mutations in the gene encoding the sodium bicarbonate cotransporter NBC1**. It manifests with:**

1. ocular abnormalities (band keratopathy, cataracts, and glaucoma often leading to blindness)
2. short stature
3. enamel defects of the teeth
4. intellectual impairment
5. and occasionally basal ganglia calcification
6. along with pRTA.

- **Autosomal dominant pattern of inheritance has been identified in a single pedigree with 9 members presenting with:**

1. hyperchloremic metabolic acidosis.
2. normal ability to acidify urine.
3. normal renal function .
4. growth retardation.

- **Clinical manifestations of Proximal RTA**

Patients with isolated, sporadic, or inherited pRTA present with failure to thrive in the 1st yr of life.

- Additional symptoms can include polyuria, dehydration (from sodium loss), anorexia vomiting, constipation, and hypotonia.
- Patients with primary Fanconi syndrome have additional symptoms, secondary to phosphate wasting, such as rickets.
- Those with systemi diseases present with additional signs and symptoms specific to their underlying disease.

- **Proximal RTA (type 2)**

Lab Findings

	Proximal RTA
Plasma potassium	Normal/low
Urine pH*	<5.5
Urine anion gap	negative
Urine ammonium	Low
Fractional bicarbonate excretion	>10-15%
Urine calcium excretion	Normal
Other tubular defects	Often present
Nephrocalcinosis	Absent
Bone disease	Common

- **Cystinosis**

Is a systemic disease caused by a defect in the metabolism of cysteine that results in accumulation of cystine crystals in most of the major organs of the body, notably the kidney, liver, eye, and brain.

- **Classification**

At least 3 clinical patterns have been described:

1- Young children type : with the most severe form of the disease (infantile or nephropathic cystinosis) present in the 1st 2 yr of life with severe tubular dysfunction and growth failure If the disease is not treated, the children develop end-stage renal disease by the end of their 1st decade.

2- Adolescents type: and is characterized by less- severe tubular abnormalities and a slower progression to renal failure.

3-adult form type: with no renal involvement also exists.

Pathogenesis

- Cystinosis is caused by mutations in the CTNS gene, which encodes a protein, cystinosin.
- Cystinosin is thought to be an H+-driven lysosomal cystine transporter.
- studies demonstrate that patients with severe nephropathic cystinosis carry mutations that lead to complete loss of cystinosin function.
- Patients with milder clinical disease have mutations that lead to expression of partially functional protein.

Clinical manifestation

Patients with nephropathic cystinosis present with clinical manifestations reflecting their pronounced tubular dysfunction including :

1. polyuria and polydipsia, growth failure, and rickets.
2. Fever: caused by dehydration or diminished sweat production.
3. skin presenttion : patients usually fair skinned and blond because of diminished pigmentation.
4. Ocular presentations include photophobia, retinopathy, and impaired visual acuity .
5. hypothyroidism.
6. hepatosplenomegaly.
7. delayed sexual maturation.

Diagnosis

- The diagnosis of cystinosis is suggested by the detection of cystine crystals in the cornea and confirmed by measurement of increased leukocyte cystine content.
  - Prenatal testing is available for at-risk families

Treatment

- Treatment of cystinosis is directed at correcting the metabolic abnormalities associated with Fanconi syndrome or chronic renal failure.
- In addition, specific therapy is available with oral cysteamine, which binds to cystine and converts it to cysteine. This facilitates lysosomal transport and decreases tissue cystine.

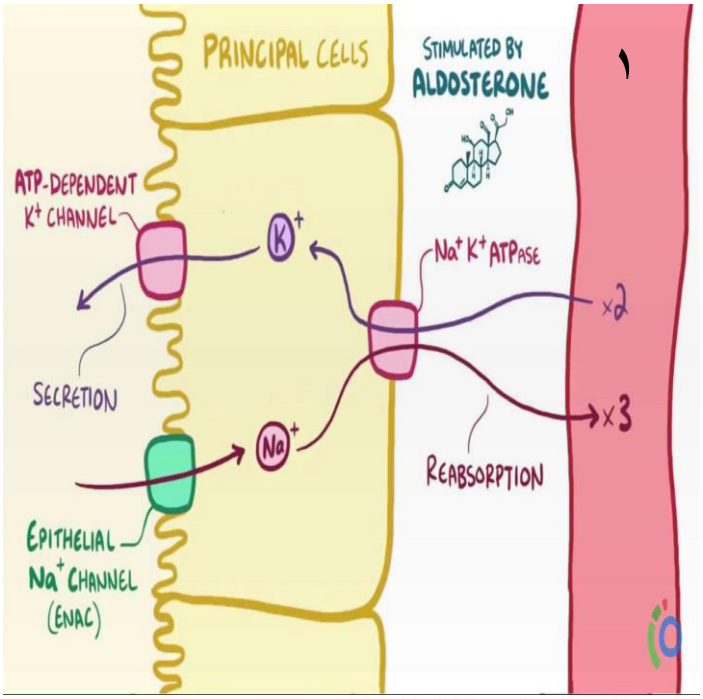
- additional therapy with cysteamine eyedrops is required for eye tissue mangment .

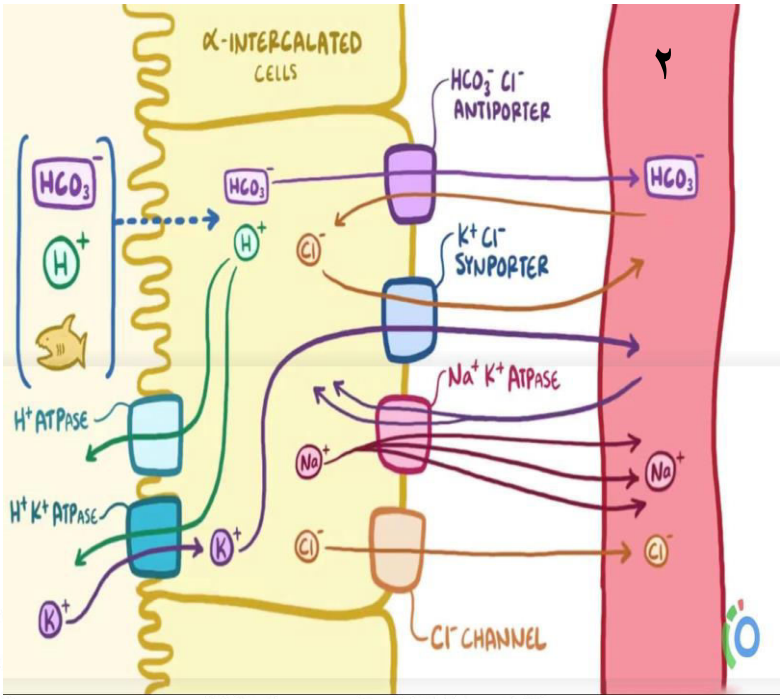
- Early initiation of the drug can prevent or delay deterioration of renal function Patients with growthfailure that does not improve with cysteamine might benefit from treatment with growth hormone.
- Kidney transplantation is a viable option in patients with renal failure.

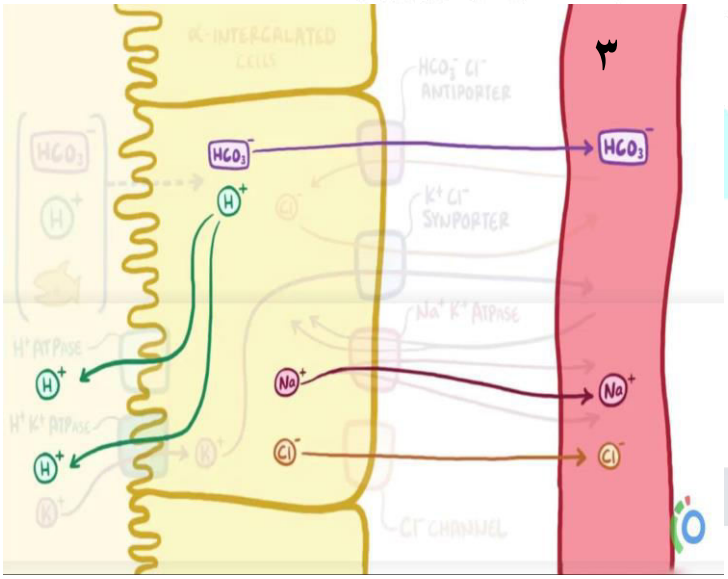
- With prolonged survival, additional complications may become evident, including central nervous system abnormalities(after age of 20years)muscle weakness, and pancreatic insufficiency.

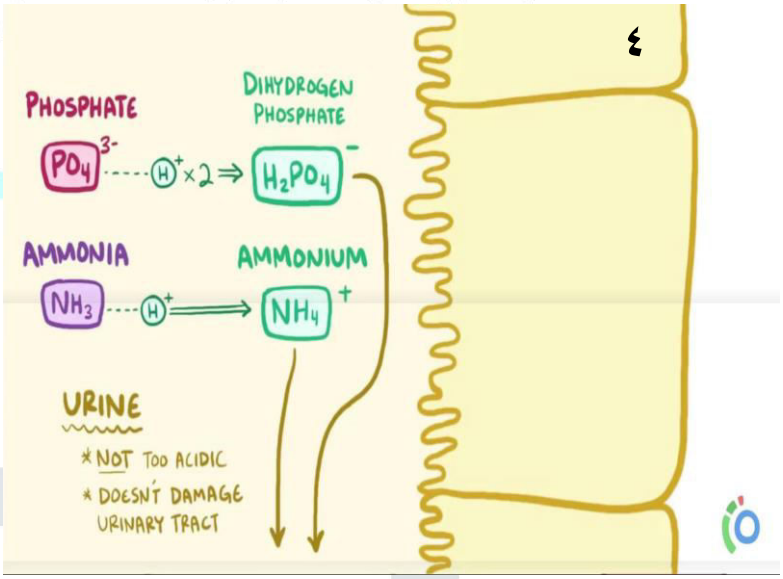
- It is unclear whether long-term cysteamine therapy will decrease these complications.

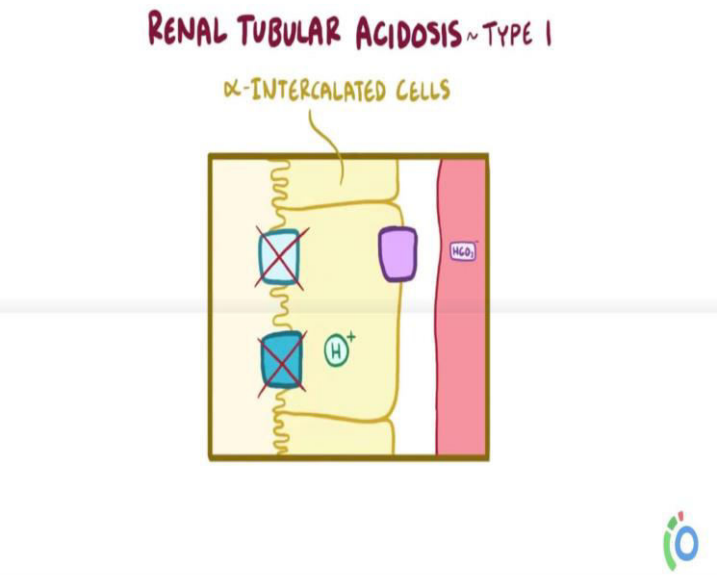
- **Type 1 (Distal RTA)**

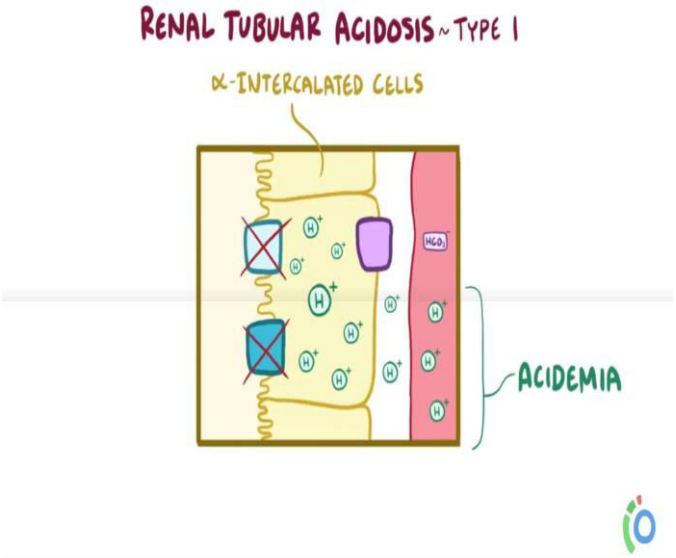


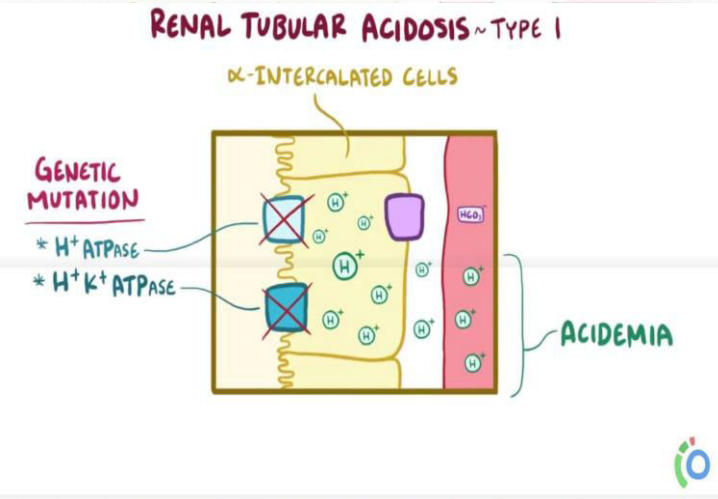


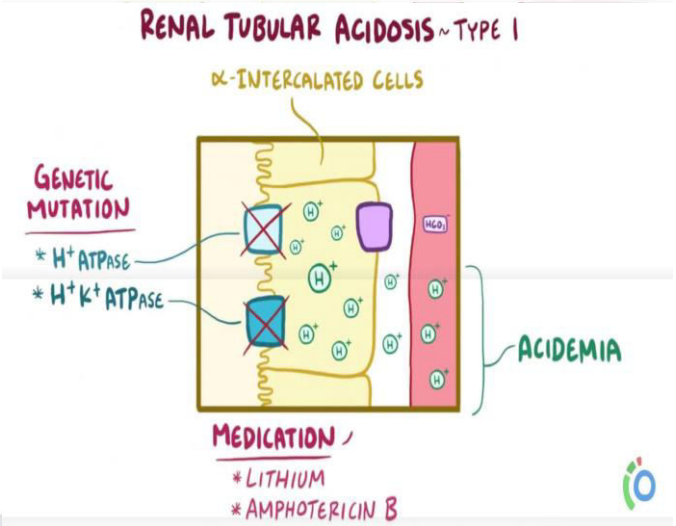


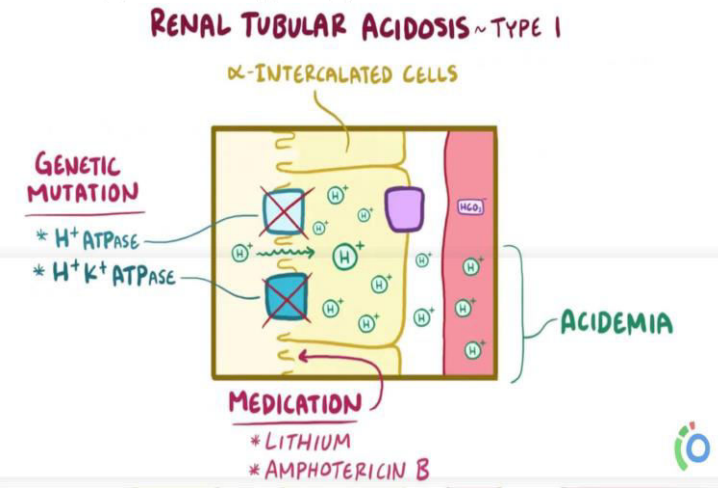


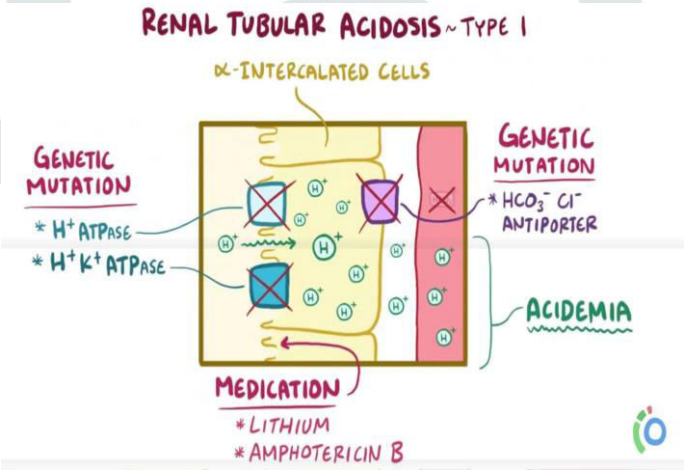










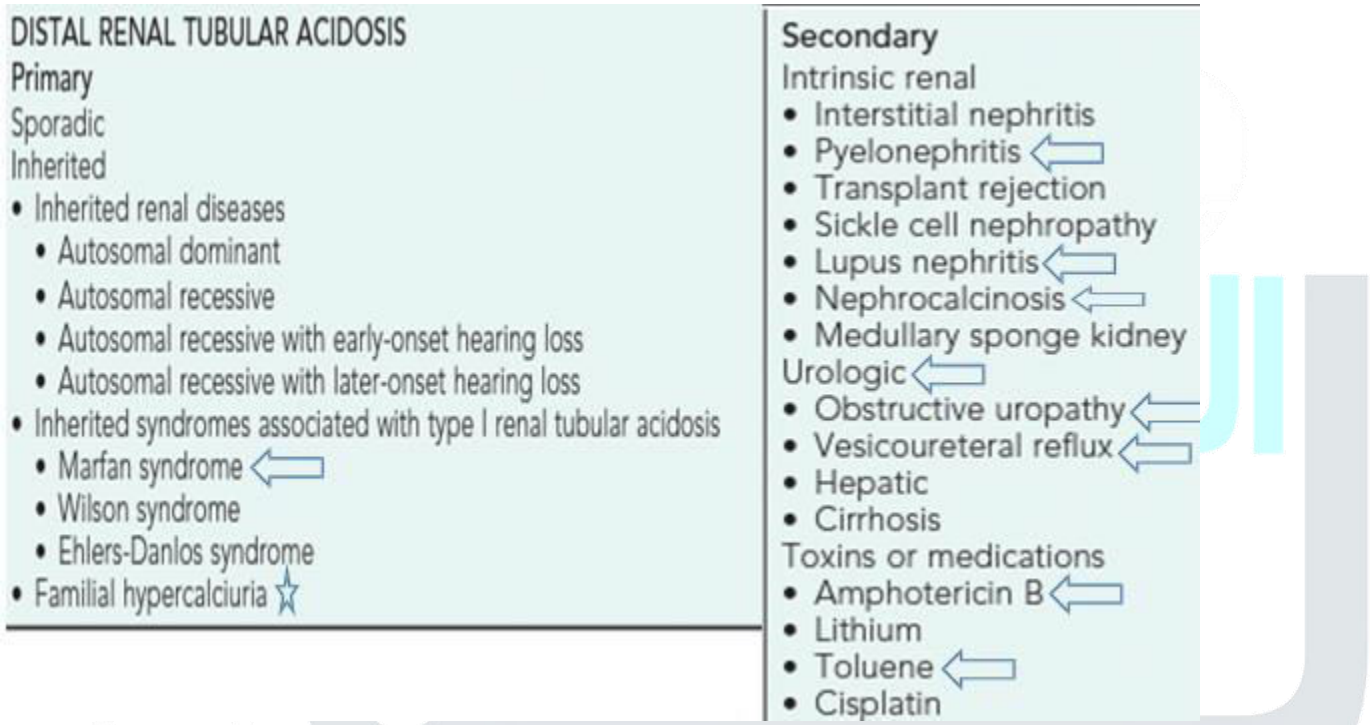


Pathogenesis

- Distal RTA can be **sporadic** or **inherited**.
- It can also occur as a complication of **inherited** or **acquired** diseases of the distal tubules.
- causes of distal RTA can result in damaged or impaired functioning of one or more transporters or proteins involved in the acidification process, including the:
  1- H+/ATPase.
  2- the HCO3 −/Cl− anion exchangers.

3- aldosterone pathway.

- Because of impaired hydrogen ion excretion, urine **pH** cannot be reduced to **<5.5** despite the presence of severe metabolic acidosis.
- Loss of sodium bicarbonate distally, owing to lack of H+ to bind to in the tubular results in increased chloride absorption and **hyperchloremia**.
- Inability to secrete H+ is compensated by increased K+ secretion distally, leading to **hypokalemia**.
- **Hypercalciuria** is usually present and can lead to nephrocalcinosis or nephrolithiasis.
- **Hypocitraturia** further increases the risk of calcium deposition in the tubules.
- **Bone disease** is common, resulting from mobilization of organic components from bone to serve as buffers to chronic acidosis.



Clinical features

Distal RTA shares features with those of pRTA, including non–anion gap metabolic acidosis and growth failure; distinguishing features of distal RTA include nephrocalcinosis and hypercalciuria.

- The phosphate and massive bicarbonate wasting characteristic of pRTA is generally absent.
- Although inherited forms are rare, 3 specific inherited forms of distal RTA have been identified, including an autosomal recessive form associated with **sensorineural deafness.**

- Medullary sponge kidney is a relatively rare sporadic disorder in children, although not uncommon in adults. It is characterized by cystic dilation of the terminal portions of the collecting ducts as they enter the renal pyramids.
- Ultrasonographically, patients often have medullary nephrocalcinosis. Although patients with this condition typically maintain normal renal function through adulthood, complications include nephrolithiasis, pyelonephritis, hyposthenuria (inability to concentrateurine), and distal RTA.
-

Feature	Type 1	Type 2
Plasma HCO3	Variable, may be <10 meq/L	14- 18 meq/L
Plasma Cl-	increased	Increased
Plasma K+	Mildly to severely decreased	Mildly decreased
Plasma anion gap	Normal	Normal
GFR	Normal or slightly decreased	Normal of slightly decreased
Fractional Excretion of HCO3	<5%	> 15%
Urine pH during acidosis	>6.0	</= 5.5

MIXED (TYPE 3) RTA :

- Infants with mild type 1 and mild type 2 defects were previously classified as type 3 RTA .
- Studies have shown that this is not a genetic entity itself , which has resulted in reclassification as a subtype of type 1 RTA that occurs primarily in premature infants .
- This pattern (once termed type 3 RTA) may be observed as a transient phenomenon in infants and young children with primary distal RTA It should be noted that this pattern of hereditary distal RTA has almost disappeared over the past two decades and does not represent a different genetic entity
- Osteopetrosis could be associated with RTA due to (carbonic anhydrase II deficiency).

Hyperkalemic (Type IV) RTA

- Type IV RTA occurs as the result of impaired aldosterone production (hypoaldosteronism) or impaired renal responsiveness to aldosterone (pseudohypoaldosteronism).
- This form is distinguished from classical dRTA and pRTA because it results in high levels of potassium in the blood instead of low levels

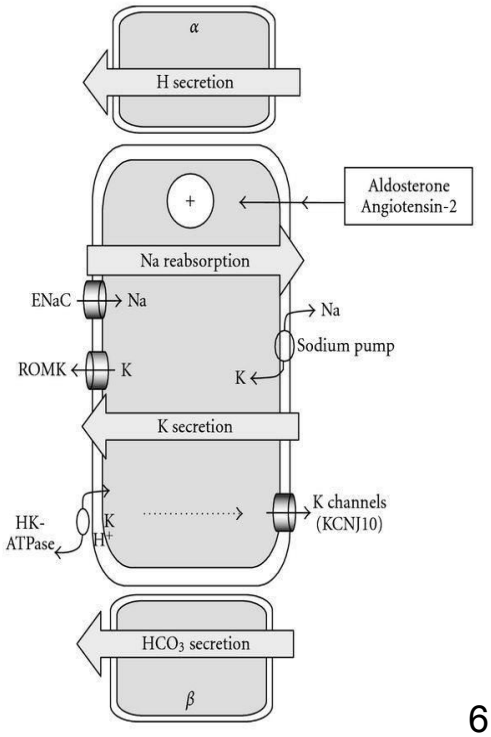
PATHOGENESIS

The collecting duct is a major site of aldosterone action;

- stimulates Na+ reabsorption and K+ secretion
- stimulates H+ secretion. (H+/ATPase)

Hypoaldosteronism, therefore, is associated with :

- Decreased Na+ reabsorption.
- Hyperkalemia àòNH3 synthesisàòNH4+ excretion
- Metabolic acidosis



Renal Tubular Acidosis

Hyperkalemic (Type IV) RTA

- Type IV RTA occurs as the result of impaired aldosterone production (hypoaldosteronism) or impaired renal responsiveness to aldosterone (pseudohypoaldosteronism).

- This form is distinguished from classical dRTA and pRTA because it results in high levels of potassium in the blood instead of low levels
- Hyperkalaemia also affects acid–base status by inhibiting ammoniagenesis which diminishes the ability of the kidneys to excrete an acid load and worsens the acidosis.

- The development of overt hyperkalemia is common in aldosterone deficient patients with other risk factors that further impair the efficiency of potassium excretion, such as renal insufficiency or the use of medications that interfere with potassium handling such as spironolactone, (ACE) inhibitors, ARBs , or renin inhibitors

Etiology :

- The causes of hypoaldosteronism include both acquired and, less often, inherited disorders, which can affect **adrenal aldosterone synthesis or renal (**and perhaps adrenal) **renin release**
- **Aldosterone deficiency** typically occurs as a result of adrenal gland disorders such as Addison disease or some forms of congenital adrenal hyperplasia.
- In children, **aldosterone unresponsiveness** is a more common cause of type IV RTA.
- This can occur transiently, during an episode of **acute pyelonephritis** or **acute urinary obstruction**, or chronically, particularly in infants and children with a history of **obstructive uropathy**.

Reduced aldosterone production
Hyporeninemic hypoaldosteronism
Renal disease, most often diabetic nephropathy
Nonsteroidal antiinflammatory drugs
Calcineurin inhibitors
Volume expansion, as in acute glomerulonephritis
Angiotensin inhibitors, such as ACE inhibitors, angiotensin II receptor blockers, and direct renin inhibitors
Chronic heparin therapy (impairs aldosterone synthesis)
Primary adrenal insufficiency
Severe illness
Inherited disorders
Congenital hypoaldosteronism (21-hydroxylase deficiency and isolated hypoaldosteronism)
Pseudohypoaldosteronism type 2 (Gordon's syndrome)

- **clinical manifestations :**
  Patients with type IV RTA can present with **growth failure** in the first few years of life. **Polyuria and dehydration** (from salt wasting) are common.

- Rarely, patients (especially those with **pseudohypoaldosteronism type 1**) present with life-threatening **hyperkalemia**.

- Patients with obstructive uropathies can present acutely with **signs and symptoms of pyelonephritis**, such as fever, vomiting, and foul-smelling urine.

- Laboratory tests reveal a **hyperkalemic non–anion gap metabolic acidosis**.

- **Elevated urinary sodium levels** with inappropriately low urinary potassium levels reflect the absence of aldosterone effect.

- Mild-to-moderate **chronic kidney disease (stages 2-3)** in most patients, with a creatinine clearance of 30-60 mL/min

Diagnostic Approach To Renal Tubular Acidosis

- **History & Examination**

- A **detailed history**, with particular attention to **growth and development**, recent or recurrent **diarrheal illnesses**, and a **family history of mental retardation**, **failure to thrive**, **end-stage renal disease**, **infant deaths**, or **miscarriages** is essential.

- **Physical examination** should determine **growth parameters** and **volume status** as well as the presence of any **dysmorphic features** suggesting an underlying syndrome.

- The first step in the evaluation of a patient with suspected RTA is to **confirm the presence of a normal anion gap metabolic acidosis**, identify **electrolyte abnormalities**, **assess renal function**, and **rule out other causes of bicarbonate loss such as diarrhea.**

- Metabolic acidosis associated with diarrheal dehydration is extremely common, and acidosis generally improves with **correction of volume depletion**.

- Patients with protracted diarrhea can **deplete their total-body bicarbonate stores** and can have persistent acidosis, despite apparent restoration of volume status.

- In instances where a patient has a recent history of severe diarrhea, full evaluation for RTA should be delayed for several days to permit adequate time for reconstitution of total-body bicarbonate stores.

- If acidosis persists beyond a few days in this setting, additional studies are indicated.

- **Serum electrolytes, blood urea nitrogen, calcium, phosphorus, creatinine**, and **pH** should be obtained by **venous puncture**

What may cause a falsely low HCO3- levels ?

Traumatic blood draws (such as heel-stick specimens), **small volumes of blood in "adult-size" specimen collection tubes**, or **prolonged specimen transport time at room temperature** can lead to **falsely low bicarbonate levels**, often in association with an **elevated serum potassium value**.

- If an **anion gap is found**, then other diagnoses (**lactic acidosis, inborn errors of metabolism, ingested toxins**) should be investigated.

- If **tachypnea** is noted, evaluation of an **arterial blood gas** might help to **rule out the possibility of a mixed acid-base disorder** primarily involving respiratory and metabolic components.
- True **hyperkalemic acidosis is** consistent with **type IV RTA**, whereas the finding of normal or low potassium suggests **type I or II.**
- Once the presence of a **non–anion gap metabolic acidosis is confirmed**, **urine pH** can help **distinguish distal from proximal causes**.
- A **urine pH <5.5** in the presence of acidosis suggests **proximal RTA**, whereas patients with **distal RTA** typically have a **urine pH >5.5**
- The **urine anion gap** ([urine Na + urine K] − urine Cl) is sometimes calculated to confirm the diagnosis of **distal RTA**.
- A **positive gap** suggests a deficiency of ammoniagenesis and, thus, the possibility of a **distal RTA**.
- A **negative gap** is consistent with **proximal** tubule bicarbonate wasting (gastrointestinal bicarbonate wasting).

Acid-loading test

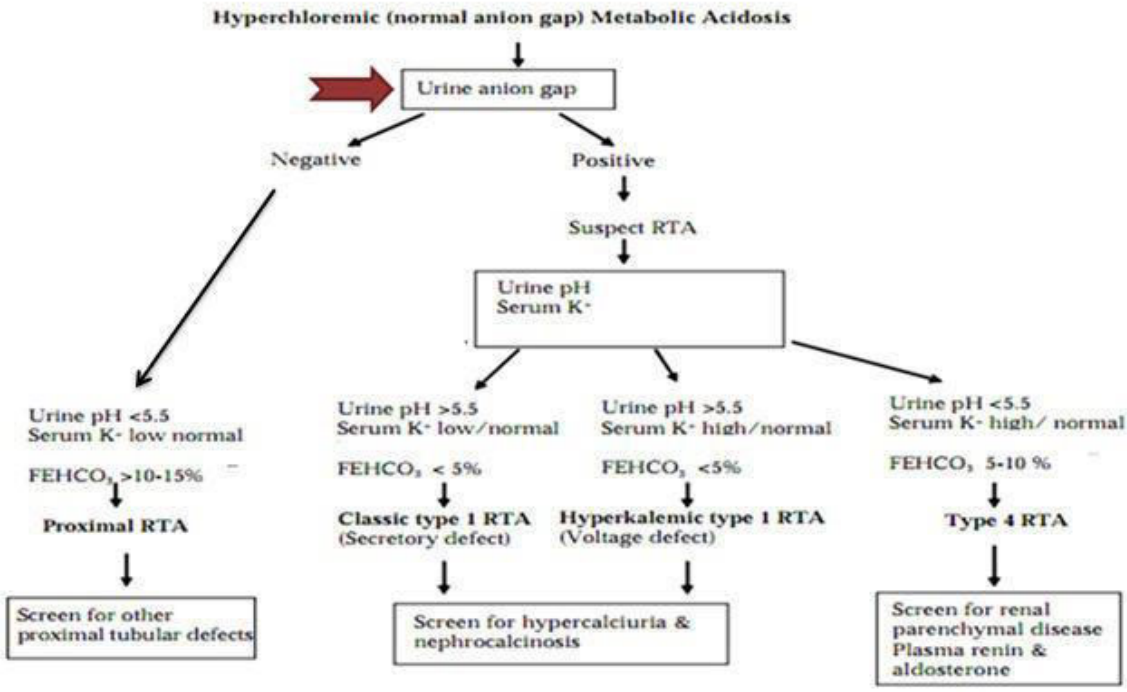
- 1.oral administrationof 0.1 g/kg (1.9 mEq/kg) of **ammonium**
- **chloride (NH4 Cl)** to **induce metabolic acidosis**.
- 2.Urine is collected hourly 2-8 hours after administration. 3.urinary pH is tested.
- **Failure to acidify urine below a pH of 5.5** supports the diagnosis of **dRTA** in which systemic acidosis is absent.
- **Urinary pH would decrease normally** in **pRTA** and hypoaldosteronism.

Fractional excretion of bicarbonate

$$\text{Fractional excretion of bicarbonate} = \frac{\text{urine bicarbonate} \times \text{plasma creatinine}}{\text{plasma bicarbonate} \times \text{urine creatinine}} \times 100$$

- The proximal tubule normally reabsorbs almost all filtered bicarbonate (fractional excretion below 5%).

*- A value **greater than 15% indicates proximal RTA** while levels are in the normal range in **distal RTA**.*



- A **urinalysis** should also be obtained to determine the presence of glycosuria, proteinuria, or hematuria, suggesting more global tubular damage or dysfunction.
- **Random or 24 hr urine calcium and creatinine measurements** will identify **hypercalciuria**, which indicates **distal RTA (type I)**
- **Renal ultrasonography**
  - structural abnormalities such as **obstructive uropathies**
  - presence of **nephrocalcinosis**
- Patients who are known to have proximal RTA or metabolic disorders associated with development of Fanconi's syndrome may appropriately be further evaluated.
- This evaluation should consist of measurement of serum phosphate/serum K, urinary glucose, urinary amino acids, and urinary phosphate excretion.

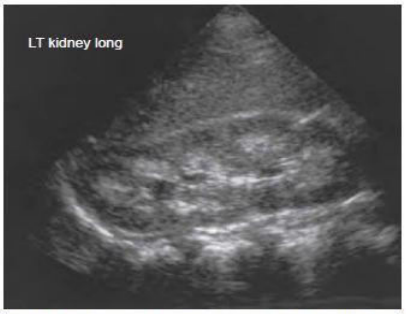


Figure 529-2 Ultrasound examination of a child with distal RTA demonstrating medullary nephrocalcinosis.

TABLE 13–7. CLINICAL AND LABORATORY MANIFESTATIONS OF VARIOUS RENAL TUBULAR ACIDOSES

	Type 1 (Classic, Distal)	Type 2 (Proximal)	Type 4 (Aldosterone Deficiency)
Growth failure	+++	++	+++
Serum potassium	Normal or low	Normal or low	High
Nephrocalcinosis	Frequent	Rare	Rare
Low citrate excretion	+++	±	±
Fractional excretion of filtered HCO_3 at normal serum HCO_3 levels	<5%	5%–10%	<10%
Daily alkali treatment (mEq/kg)	1-3	5-20	1-3
Daily potassium requirement	Decreases with correction	Increases with correction	
Urine pH	>5.5	<5.5	<5.5
Presence of other tubular defects	Rare	Common	Rare

Treatment :

The mainstay of therapy in all forms of RTA is bicarbonate replacement.

- Patients with pRTA often require large quantities of bicarbonate, up to 20 mEq/kg/24 hr, in the form of sodium bicarbonate or sodium citrate (Bicitra or Shohl solution)
- The base requirementfor distal RTAs in the range of2-4 mEq/kg/24 hr, although patients' requirements can vary.
- Patients with distal RTA should be monitored for development of hypercalciuria
- Those with symptomatic hypercalciuria can require thiazide diuretics to decrease urine calcium excretion.
- Patients with Fanconi syndrome usually requirephosphate supplementation.
- Patients with type IV RTA can require chronic treatment for hyperkalemia with sodium-potassium exchange resin (Kayexalate).
- Appropriate therapy for hypoaldosteronism varies with the cause of the hormone deficiency.

Prognosis:

- Prognosis of RTA depends to a large part on the nature of any existing underlying disease. Patients with treated isolated proximal or distal RTA generally demonstrate improvement in growth, provided serum bicarbonate levels can be maintained in the normal range.

- Patients with systemic illness and Fanconi syndrome can have ongoing morbidity with growth failure, rickets, and signs and symptoms related to their underlying disease.

Rickets Associated with RTA

- **Rickets** may be present in primary RTA, particularly in **pRTA (type II)**.

- **Hypophosphatemia** and **phosphaturia** are common in RTA , which are also characterized by hyperchloremic metabolic acidosis, various degrees of bicarbonaturia, and, often, hypercalciuria and hyperkaluria.

- **Bone demineralization without overt rickets** usually is detected in **distal RTA (type I) ,** which probably relates to **dissolution of bone**, because the **calcium carbonate in bone serves as a buffer against the metabolic acidosis** due to the hydrogen ions retained by patients with RTA.

- This metabolic bone disease may be characterized by bone pain, growth retardation, osteopenia, and, occasionally, pathologic fractures.

- the circulating levels of 1,25(OH)2D in patients with either type of RTA are generally normal unless patients with RTA have chronic renal insufficiency, **serum 1,25(OH)2D levels are reduced in relation to the degree of renal impairment**.

- "**double osteomalacia**" may be evident when patients with either type of RTA also have vitamin D deficiency.

Management

- Administration of **sufficient bicarbonate to reverse acidosis** reverses bone dissolution and the hypercalciuria that is common in **distal RTA**.
- **Proximal RTA** is treated with both **bicarbonate and oral phosphate**
- supplements to heal rickets.
- **Vitamin D is required to offset the secondary hyperparathyroidism** that complicates oral phosphate therapy.
- Following therapy, growth in patients with type II (proximal) RTA is greater than in patients with primary Fanconi syndrome.

Hypoxic Ischemic Encephalopathy (HIE)

Definitions

Hypoxic-Ischemic Encephalopathy : Abnormal neurologic behavior in the neonatal period arising as a result of a *hypoxic-ischemic event*.

- The severity of hypoxic-ischemic encephalopathy (HIE) can be defined depending on *symptoms and signs*

. Mild
. moderate
. severe

- ***Hypoxia or Anoxia :*** Partial (hypoxia) or complete (anoxia) lack of oxygen in the brain or blood.
- ***Asphyxia :*** This is the state in which placental or pulmonary gas exchange is compromised or ceases typically producing a combination of *progressive hypoxemia and hypercapnia.*
- ***Ischemia*** : This is reduction (partial) or cessation (total) of blood flow to an organ (such as the brain), which compromises both *oxygen and substrate* delivery to the tissue.

Incidence

2-4 cases per 1000 births

Mortality rate

- Severe HIE the mortality rate has been reported to be 50-75%
- Most deaths (55%) occur in the first week of life due to multiple organ failure

SELECTIVE VULNERABILITY

A number of factors influence the distribution of brain injury, summarized as follows:

. Cellular susceptibility
. Maturity
. Vascular territories
. Regional susceptibility
. Type of hypoxic-ischemic insult

Cellular Susceptibility **:** The neuron is the most sensitive cellular element to hypoxic-ischemic insult, followed by cells cerebral vasculature.

Maturity **:** Gestational age plays an important role in the changing susceptibility of cerebral structures to hypoxic-ischemic insult.

. Hypoxic-ischemic insult before 20 weeks' gestational age, polymicrogyria
. during midgestation (26 to 36 weeks) predominantly damage white matter, leading to periventricular leukomalacia
. Insults at term (35 weeks and beyond) predominantly damage deep gray matter (posterior putamen and ventrolateral nucleus of the thalamus).

Vascular Territories

Watershed injury : refers to tissue damage that occurs in regions that are most vulnerable to reduction in cerebral perfusion

- These tissues are at the <u>furthest points of arterial anastomoses</u> and are exposed to damage when perfusion pressure falls, usually as the result of impaired cardiac output.

- In the term brain,
  - the parasagittal region
  - The paracentral gyrus → are particularly liable to watershed injury
  - The motor cortex

  ☒ *this accounts for the observation that <u>spastic cerebral palsy</u> is the most common major sequela to hypoxic-ischemic insult at term.*
  - the hippocampus, temporal lobe, and occipital lobes are most resistant to this type of insult.

Types of Hypoxic-Ischemic Insult

- **Acute total asphyxia**

- *This produced injury to the*
- *Thalamus*
- *brainstem*
- *spinal cord structures*

- **partial asphyxial insult lasting 1 to 5 hours**

- *This produced damage predominantly in the*
- *cerebral hemispheres*
- *basal ganglia*
- *cerebellum.*

PATHOPHYSIOLOGY

- Early or primary neuronal damage occurs as a result of <u>*cytotoxic changes*</u> due to:

. failure of the microcirculation
. inhibition of energy-producing molecular processes
. increasing extracellular acidosis
. and failure of Na+/K+-adenosine triphosphatase (ATPase) membrane pumps

☒ which results in <u>*excessive leakage of Na+ and Cl-*</u> into the cell with consequent accumulation of intracellular water <u>*(cytotoxic edema)*</u>

<u>*- Free radical*</u> production is also initiated, which further compromises neuronal integrity

- If not reversed, these processes lead to neuronal death within a short time of the acute insult

The primary physiological processes that lead to HIE

- Systemic hypoxemia . Reduced cerebral blood flow (CBF)

Early compensatory adjustments

Hypoxia and hypercapnia

- Increase in the CBF

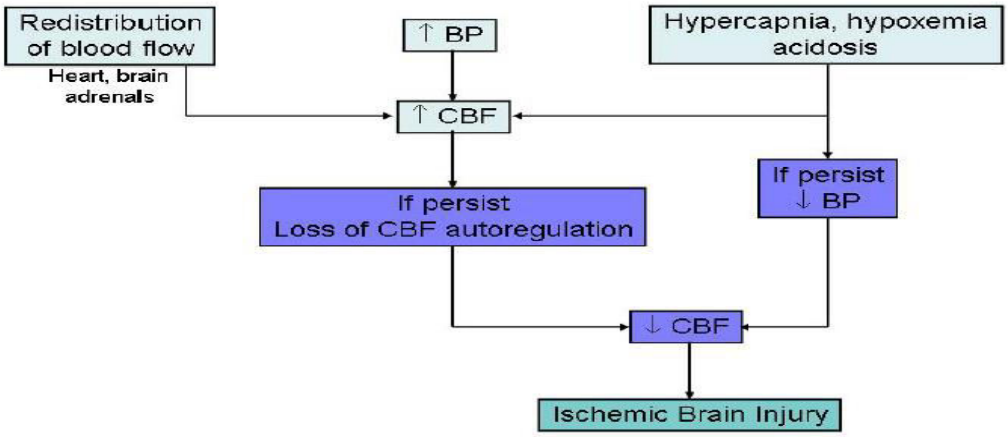
- Increase cardiac output
- BP increase

Early compensatory adjustments fail

BP falls

- CBF falls below critical levels

- Brain suffers from diminished blood supply
- Lack of sufficient oxygen to meet its needs.

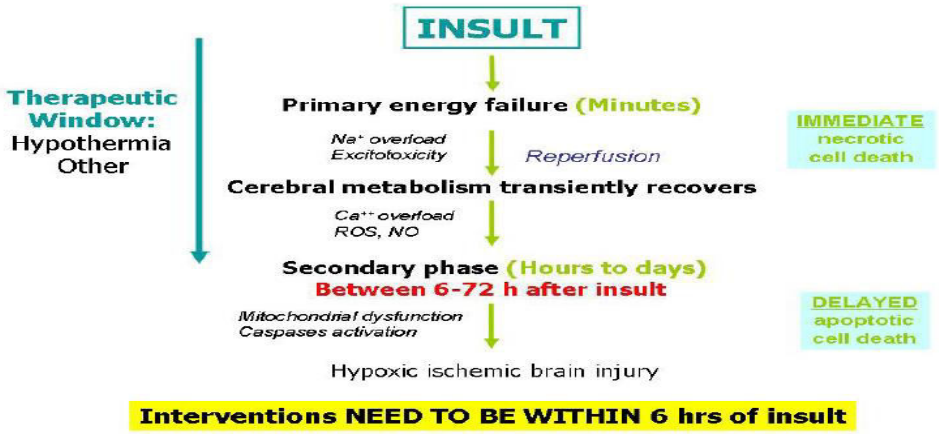


During the early phases of brain injury, *brain temperature drops*

- Local release of neurotransmitters, such as (GABA) increase
- Reduce cerebral oxygen demand, transiently minimizing the impact of asphyxia

The magnitude of the final neuronal damage depends

- Initial insult
- Damage due to energy failure
- Reperfusion injury
- Apoptosis



HIE History

AAP Criteria

- Profound metabolic acidosis
- Mixed acidemia (pH <7) in an umbilical artery blood sample
- Persistence of an Apgar score of 0-3 for longer than 5 minutes
- Neonatal neurological sequelae (e.g., seizures, coma, hypotonia)

History

AAP Criteria

- Multiple organ involvement (e.g., kidney,lungs, liver, heart, intestines)

On rare occasions

- Difficulties with delivery
- Particularly problems with delivering the head

HIE Physical Examination

Mild HIE

- Muscle tone may be slightly increased
- Deep tendon reflexes may be brisk during the first few days
- Poor feeding, irritability, or excessive crying or sleepiness ,may be observed.
- By 3-4 days of life, the CNS examination findings become normal

Moderate HIE

- Lethargy
- Significant hypotonia
- Diminished deep tendon reflexes.
- Grasping, Moro, and sucking reflexes may be sluggish or absent.

- The infant may experience periods of apnea.
- Seizures may occur within the first 24 hours of life.
- Full recovery within 1-2 weeks----better long-term outcome.

Severe HIE

- Stupor or coma is typical
- Breathing may be irregular
- Generalized hypotonia and depressed deep tendon reflexes are common.
- Neonatal reflexes are absent.
- Disturbances of ocular motion
- Nystagmus
- Pupils may be dilated, fixed, or poorly reactive to light

Classification of HIE by Sarnat 1976

Stage I,II,III

ETIOLOGY

Fetal hypoxia may be caused by *various disorders in the mother, including :*

(1) *inadequate oxygenation of maternal blood*

   (1) hypoventilation during anesthesia

   (2) cyanotic heart disease

   (3) respiratory failure

   (4) or carbon monoxide poisoning

(2) *low maternal blood pressure*

   (1) acute blood loss

   (2) spinal anesthesia

   (3) compression of the vena cava and aorta by the gravid uterus

(3) *inadequate relaxation of the uterus to permit placental filling* as a result of uterine tetany caused by the administration of excessive oxytocin

(4) *premature separation of the placenta*

(5) impedance to the circulation of blood through the umbilical cord as a result of *compression or knotting of the cord*

(6) *placental insufficiency* from toxemia or postmaturity

After birth, hypoxia may be caused by:

(1) *failure of oxygenation as a result of severe forms*

- cyanotic congenital heart disease
- severe pulmonary disease

(2) anemia severe enough to lower the oxygen content of the blood

- severe hemorrhage
- hemolytic disease

(3) shock severe enough to interfere with the transport of oxygen to vital organs from

- overwhelming sepsis
- massive blood loss
- intracranial or adrenal hemorrhage

Risk Factors

Preconceptual	Antepartum	Intrapartum
IDDM	Severe preeclampsia	Breech/Malpresentation
Thyroid disease	Placental abruption	Cord prolapse
Fertility treatments	Multiples	Instrumentation
Nulliparity	Antepartum hemorrhage	Stat C-section
Advanced maternal age	IUGR	Induction
		Maternal pyrexia

Multiorgan Systemic Effects of Asphyxia

- Central nervous system
  - Hypoxic-ischemic encephalopathy
  - infarction
  - intracranial hemorrhage
  - seizures,
  - cerebral edema
  - Hypotonia
  - hypertonia
- Cardiovascular
  - Myocardial ischemia
  - poor contractility,
  - tricuspid insufficiency
  - hypotension
- Pulmonary
  - Pulmonary hypertension
  - pulmonary hemorrhage
  - respiratory distress syndrome
- Renal
  - Acute tubular or cortical necrosis

- Adrenal : Adrenal haemorrhage

- Gastrointestinal
  - Perforation
  - ulceration
  - hemorrhage
  - necrosis

- Metabolic
  - Inappropriate secretion of antidiuretic hormone
  - hyponatremia
  - hypoglycemia
  - Hypocalcemia - myoglobinurea
- Subcutaneous fat necrosis

- Hematology
  - Disseminated intravascular coagulation

Differential Diagnosis

- Inborn errors of metabolism
- Neuromuscular disorders
- Neonatal myopathies
- Brain tumors
- Developmental defects
- Infections

Work-up

-Serum electrolytes

-In severe cases

- Daily assessment of serum electrolytes are valuable
- SIADH

-Renal function studies

-Cardiac and liver enzymes

-Coagulation system evaluation

-ABG

HIE Imaging Study

- MRI

- Loss of cerebral gray and white matter differentiation
- Basal ganglia or thalamus injury
- Parasagittal cerebral injury
- Decreased signal in the posterior limb of the internal capsule

- **Imaging**

- Head CT scanning

- Cerebral edema
- Ventricular hemorrhage

- Echocardiogram

- Myocardial contractility
- Structural heart defects

- EEG

- Continuous low voltage pattern
- Seizures

Treatment

- Maintain adequate ventilation.
- Maintain adequate perfusion:
- Maintain the mean blood pressure (BP) above 35-40
- Maintain adequate metabolic status
- Seizures should be treated with : phenobarbital or lorazepam, phenytoin can be added if persistent

Hypothermia Treatment

- Mild hypothermia 3-4°C below the baseline temperature
- Mechanism of action :
  - Reduced metabolic rate
  - Energy depletion
  - Decreased excitatory transmitter release
  - Reduced ion flux
  - Reduced apoptosis
  - Reduced vascular permeability, edema, and
  - disruptions of blood-brain barrier functions.

-Timing of initiation of hypothermia therapy:

- Cooling must begin early, within 1 hour of injury
- Favorable outcome may be possible if the cooling begins within 6 hours after injury

<u>The greater the severity of the initial injury, the longer the duration of hypothermia needed for optimal neuroprotection</u>

-Selective head cooling

- Acap (CoolCap) with channels for circulating cold water is placed over the infant's head, and a pumping device facilitates continuous circulation of cold water. Nasopharyngeal or rectal temperature is then maintained at 34-35°C for 72 hours

-Whole body cooling

- Infant is placed on a commercially available cooling blanket, through which circulating cold water flows, so that the desired level of hypothermia is reached quickly and maintained for 72 hours

-Surgical Care

- Posterior cranial fossa hematoma, surgical drainage may be life saving if no additional pathologies are present

-Consultations

- Pediatric neurologist should help assist in the management of seizures, interpretation of EEG

-Diet

- Nothing by mouth (NPO) during 1st 3 DOL or until the general level of alertness and consciousness improves
- Begin trophic feeding

- Begin trophic feeding

- Monitor for NEC :
  - Abdominal girth
  - Gastric residuals
  - Stools

-PT

PREVENTION

PRIMARY PREVENTION

- RESUSCITATION :following steps should be taken in sequence until the infant responds adequately:
  - Provide tactile stimulation.
  - Open airway. Extend the infant's neck and give chin support.
  - Inflate lungs Use a self-inflating bag and mask if spontaneous respirations have not been established by 30 to 60 seconds
  - Consider giving the infant five lung inflations (pressure of 30 cm of water in a term infant) for 2 to 3 seconds each.
  - Ventilate lungs. If spontaneous respiration has not been established after five inflations, start intermittent positive pressure ventilation at 30 breaths/min.
  - Intubate. If the infant has not improved after 2 minutes of intermittent positive pressure ventilation
  - Use chest compression. If the heart rate is <60 bpm despite adequate ventilation. Coordinate compressions and ventilation in a 3:1 to achieve 90 compressions and 30 breaths per minute.
  - Administer drugs. Epinephrine (10 µg/kg or 0.1 mL/ kg of 1:10,000) should be given down the endotracheal tube if the heart rate remains below 60 beats/min, and can be repeated up to three times.
  - Epinephrine and other drugs can also be given through an umbilical catheter.
  - volume expansion with normal saline
  - Intramuscular naloxone (200 µg) is indicated if the infant fails to breathe spontaneously and if the mother has received opiates for pain relief within 4 hours before delivery.

- **Conditions in Which the Need for Resuscitation at Birth May Be Anticipated:**

Maternal

- Toxemia (eclampsia)
- Diabetes mellitus
- Drug addiction
- Cardiovascular disease
- Infectious disease
- Collagen vascular disease

Uteroplacental

- Placental abruption
- Umbilical cord prolapse
- Placenta previa
- Polyhydramnios
- Premature rupture of the membranes

Intrapartum Factors

- Isoimmunization
- Multiple birth
- Abnormal presentation
- Precipitous delivery
- Fetal distress
- Thick meconium staining
- Prolonged labor
- Difficult forceps delivery
- Intrauterine growth restriction
- Prematurity

Prevention

Allopurinol: is an inhibitor of xanthine oxidase and has free radical scavenging action

High-dose phenobarbital : (40 mg/kg) was associated with a significant reduction in severe neurodevelopmental disability

Excitatory amino acid (EAA) antagonists : Magnesium sulfate ($MgSO_4$) is an *N*-methyl-d-aspartate receptor antagonist and has been proposed to be an effective agent for brain protection

Prognosis

Good Prognostics

- Normal EEG at 7 DOL

Poor prognostics

- No spontaneous respiratory effort within 20-30 minutes
- Seizures is an ominous sign
- Abnormal clinical neurological findings >7-10 DOL
- Persistent feeding difficulties -Poor head growth during the postnatal period

Newborn Resuscitation

Neonatal Resuscitation
Newborn Resuscitation
Delivery room Resuscitation

Indicates the transition from fetal to extra uterine life .

Physiologic changes occur in this transition

Series of actions, used to assist newborn babies who have difficulty with making the physiological 'transition' from the intrauterine to extrauterine life , Assists babies who fail to initiate or sustain regular breathing at birth.

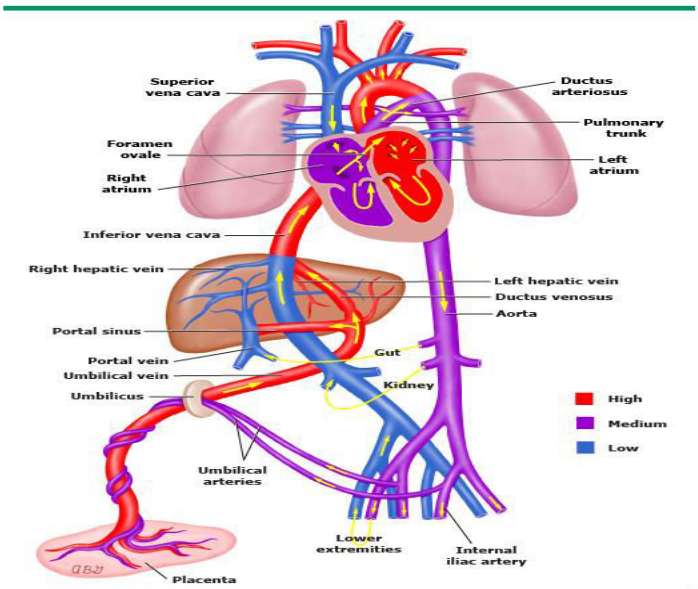
The fetus circulation :

Placenta [Maternal blood] >> to umbilical vein then 50% will go to the liver then hepatic vein [portal circulation] and 50% to the ductus venosus then to the Inferior vena cava >> to the Right atrium :

1- 30% will go to the left atrium through the foramen ovale then to the aorta (well oxygenated)

2- 70% to the right ventricle then the pulmonary artery , from there 10% goes to the lung for nutrition and 90% to the aorta through ductus arteriosus .

- Three shunts exist to permit much of the blood returning to the right side of the heart to continue directly into the systemic circulation, by passing the pulmonary circulation; these shunts are (a) the foramen ovale in the atrial septum, (b) the interventricular shunt, and (c) the ductus arteriosus.



The degree of oxygen saturation is indicated by shading, as explained in the figure key.

So, The pathways of blood within the embryo and fetus :

(1) the umbilical arteries carry deoxygenated blood to the placenta where oxygen and nutrients are transferred from the maternal circulation by diffusion,
(2) umbilical vein returns oxygenated nutrient-laden blood to the liver and to the inferior vena cava,
(3) the ductus venosus in the liver shunts some of the oxygenated blood directly to the inferior vena cava without passing through the hepatic capillary beds

- **In utero, most of the blood flow is shunted away from the lungs and directed to the placenta where fetoplacental gas exchange occurs .**

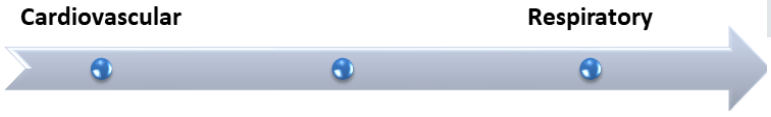
Fetal oxygenation

- The intrauterine oxygen tension is low compared to that in extrauterine life, this low fetal oxygen tension maintains the architecture of the fetal circulation
- The highest oxygenated fetal blood is found in the umbilical vein with PO_2 as high as 55±7 mmHg .
- Oxygen saturation decreases when mixed with venous return, so that blood returning to the placenta will have a PO_2 of 15 to 25 mmHg.
- Despite the low oxygen tension in the fetus, there is adequate tissue oxygenation because of the following factors: - Fetal hemoglobin – Decreased fetal oxygen consumption

fetal metabolism and oxygen consumption are decreased because:

- The fetus does not need to maintain thermoregulation because the thermal environment is maintained by the mother.
- In the fetus, many physiologic functions are reduced, including respiratory effort, gastrointestinal digestion and absorption, and renal tubular reabsorption (due to the low glomerular filtration rate). These changes reduce tissue oxygen consumption.

Physiological changes at birth



Circulatory changes : The transition of circulation , occuring between the fetal and neonatal periods .

1- Clamping of the umbilical cord : Until recent years , a common practice has been to clamp the umbilical cord soon after birth to quickly transfer the infant to the neonatal team for stabilization . This Immediate clamping was deemed particularly important for infants at high risk for difficulty with transition and those more likely to require resuscitation , such as infants born preterm , During the 2010 COSTR review , evidence began to emerge suggesting that DCC : delayed cord clamping might be beneficial for infants who did not need immediate resuscitation at birth .

- The 2015 ILCOR systematic review confirms that DCC is associated with less intraventricular hemorrhage of any grade , higher blood pressure and blood volume , less need for transfusion at birth , and less necrotizing enterocolitis .

** From an article that Reprinted with permission of the american heart association

- ILCOR : International liaison committee on resuscitation

- The only negative consequence appears to be a slightly increased level of bilirubin : phototherapy .

- These findings have led to national recommendations that DCC be practiced when possible.

- *Clamping of the umbilical cord* : Diminution of blood returning to the right ventricle :Eliminates the low – pressure system of the placenta : Rise in the neonatal systemic blood pressure : decreased venous return from the placenta : decreases atrial blood pressure !

- AS BREATHING begins , increasing inspiratory pressure , expand the alveolar air spaced , establishes FRC , stimulation of surfactant release , air replaces lung fluid , maintaining the functional residual capacity . And the lung must transition rapidly to become the site for gas exchange , otherwise : Cyanosis & hypoxia rapidly develop .

  Fluid leaves the lung , In part , through the trachea , it is either swallowed or squeezed out during vaginal delivery [thoracic squeezing] . The pulmonary lymphatic and venous systems reabsorb the remaining fluid .

- Most normal infants require little pressure to spontaneously open the lungs after birth [5-10 cm H2O] .
  - With the onset of breathing , pulmonary vascular resistance decreases 8- 10 folds , partly a result of the mechanics of breathing , and partly a result of the elevated arterial oxygen tensions .

- The increased blood flow to the lungs increases the volume of pulmonary venous blood returning to the left atrium .

- Left atrial pressure Now > Right atrial pressure >> The foramen ovale closes !

- As the flow through the pulmonary circulation increases and arterial oxygen tensions rise , The ductus arteriosus begins to constrict .

- In term infant , this constriction functionally closes the ductus arteriosus within 1 day after birth .

- A permanent closure requires thrombosis and fibrosis , a process that may take several weeks.

- In a premature infant , the ductus arteriosus is less sensitive to the effects of oxygen , if circulating levels of vasodilating prostaglandins are elevated , may remain patenet .

- This patency is a common problem in a premature infant with >> RDS !

- ***The ductus arteriosus mechanism of closure :***
  At birth the mature lung , initiation of breathing and washing of prostaglandins (vasodilators) and increase in O2 leading to vasoconstriction , closure of the DA

- **Late changes :**
  During the first few months after birth some vascular channels are transformed into ligaments , these are the following :

  1. Ductus Arteriosus : becomes the ligament arteriosum.
  2. Ductus Venosus : closes at 7-8 days to become ligamentum venosum
  3. Left umbilical vein : becomes the ligament teres of the liver .
  4. Umbilical arteries : become the lateral umbilical ligaments .

Neonatal Difficulties :

1- Lack of respiratory effort
2- Blockage of the airways
3- Impaired lung function
4- Persistent increased pulmonary vascular resistance
5- Abnormal cardiac structure &/Or function

Problems with preterm babies :

1- Immature lungs- difficult to ventilate and also more vulnerable to injury by PPV;
2- Immature blood vessels in the brain that are prone to hemorrhage;
3- Thin skin & large BSA ⇨ Rapid heat loss;
4- Increased susceptibility to infection;
5- ↑ risk of hypovolemic shock related to small blood volume

- Neonatal resuscitation skills are essential for all health care providers who are involved in the delivery of newborns. The transition from fetus to newborn requires intervention by a skilled individual or team in approximately 10% of all deliveries
- Most newly born babies are delivered vigorous
- Approximately 10% [½ have no risk] of newborns require some assistance to begin breathing at birth.
- Less than 1% require extensive resuscitation measures such as cardiac compressions and medications.
- Although most newly born infants successfully transition from intrauterine to extrauterine life without special help , but because the large total number of births , a significant number will require some degree of resuscitation .
- *The aim of resuscitation is to prevent neonatal death and adverse long term neurodevelopmental sequelae associated with perinatal asphyxia. : decrease mortality and morbidity from hypoxic-ischemic injury to the tissues & reestablish spontaneous respiration and cardiac output.*

Anticipation of Resuscitation need :

Readiness for neonatal resuscitation requires :

- Assessment of perinatal risk
- A system to aasemble the appropriate personnel based on that risk
- An organized method for ensuring immediate access to supplies and equipment
- Standarization of behavioral skills that help assure effective teamwork and communicaton.

- Therefore, at every birth, no matter how "low risk , because a newborn The need for resuscitation of the newborn infant at birth cannot always be anticipated nor predictedwithout apparent risk factors may unexp", suitable equipment and staff must be available and prepared to resuscitate the newborn infant. [at least 1 person who can perform the initial steps of resuscitation and whose only responsibility is care of the newborn , in the presence of significant perinatal risk factors : ++ the likelihood of the need for resuscitation .

- However sometimes risk factors are poor predictors of birth asphyxia.

- Up to ½ of newborns who require resuscitation have no identifiable risk factors before birth. Therefore it is not enough to be prepared only in cases where one or more risk factors are present

Risk factors are associated with a greater likelihood of having difficulty making a successful transition and of requiring resuscitation :

Maternal Risk Factors:

- Prolonged rupture of membranes (greater than 18 hours)
- Bleeding in second or third trimester
- Pregnancy induced hypertension or Chronic Hypertension.
- Substance abuse.
- Drug therapy (e.g. lithium, magnesium, adrenergic blocking agents, narcotics)
- Diabetes mellitus
- Chronic illness (e.g. anaemia, cyanotic congenital heart disease)
- Maternal pyrexia
- Maternal infection or Chorioamnionitis
- Heavy sedation
- Previous fetal or neonatal death
- No prenatal care

Fetal Risk Factors:

- Multiple gestation (e.g. twins, triplets)
- Preterm gestation (especially less than 35 weeks)
- Post term gestation (greater than 41 weeks)
- Fetal growth restriction
- Alloimmune haemolytic disease (e.g. anti-D, anti-Kell, especially if fetal anaemia or hydrops fetalis present)
- Polyhydramnios and oligohydramnios
- Reduced fetal movement before onset of labour
- Congenital abnormalities which may effect breathing, cardiovascular function or other aspects of perinatal transition
- Intrauterine infection
- Hydrops fetalis.
- Large for dates.

Intrapartum Risk Factors:

- Non reassuring fetal heart rate patterns on cardiotocograph (CTG)
- Abnormal presentation
- Prolapsed cord
- Prolonged labour (or prolonged second stage of labour)
- Antepartum haemorrhage (e.g. abruption, placenta praevia, vasa praevia)
- Meconium in the amniotic fluid
- Narcotic administration to mother within 4 hours of birth
- Forceps birth
- Vacuum-assisted (vento-use) birth
- Maternal general anaesthesia

Newborn Resusciation

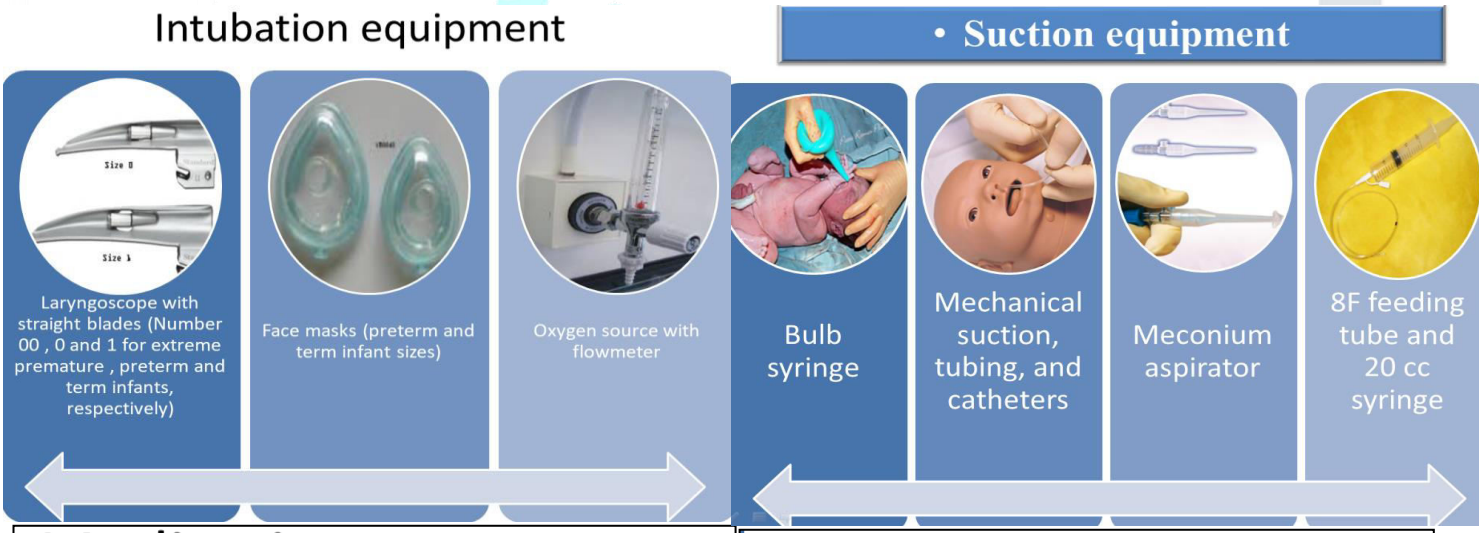
Preparation

1. **Personnel :**

- Every Birth attendant must be trained in Resusitaion.
  - At least two trained people are required for adequate resuscitation involving positive pressure ventilation and chest compressions. Therefore, always call for help.
  - The most senior person available needs to co-ordinate resuscitation.
  - Each person must have a dedicated job. For exa. with three people, one should be solely responsible for airway, one solely responsible for chest compressions and the third person should co-ordinate the resuscitation and administer medication as necessary.

2. Check equipment :

- Every Birth must have resuscitation equipment and supplies in perfect condition.
- Resuscitation equipment should be checked at least daily and after each usage.
- When use is anticipated at a birth recheck equipment including(medical air and oxygen supply, suction, positive pressure devices, resuscitation equipment, largyngoscope, and endotracheal tubes).
- When no equipment is available, mouth to mouth-and-nose breathing should be done.



Medications
Dextrose solution 10 percent
Epinephrine (0.1 mg/mL)
Isotonic solution
Naloxone hydrochloride (0.4 mg/mL)
Needles , Syringes
Umbilical vessel catheterizations supplies
Sterile gloves, antiseptic prep solution, umbilical catheter.

Others	• Radiant warmer • Warm towels • Cardiac monitor • Pulse oximeter and probe • Oropharyngeal airways
Additional equipment for delivery of preterm infants	• Compressed air source • Oxygen blender • Transport incubator

3. Communication : {IS vital to smooth resuscitation }

- With anaesthetic and obstetric staff regarding maternal condition, fetal condition, maternal therapies.
- If time permits, meet the family before the birth.

4.Environment :

- Prevention of heat loss is important.
- Where possible deliver infant into a warm draft free environment.
- The ambient temperature of the room should be at least 26 C for very preterm infants.

Assessment and recognition of the problem

- The need for resuscitation must be recognized before the end of the first minute of life which is when the first Apgar score is taken.
- The most important indicator that resuscitation is needed is failure to BREATHE after birth so, if the baby does not breathe, resuscitation must be started immediately.

1.Breathing :

- The newly born infant should establish regular respirations in order to maintain HR > 100 bpm.
- The **Baby's Cry** is the most obvious sign that there is adequate ventilation after the birth beside in a crying newborn the heart rate is normal.
- Breathing immediately after birth may be irregular but is usually still sufficient for adequate ventilation. However, gasping (occasional breaths with long pauses in between) is not sufficient.
- If the newborn does not cry or breathe at all, or is gasping within 30 seconds of birth, and after being dried, the essential steps of resuscitation should be taken immediately.

2.Heart Rate

The HR should be > 100 bpm in a well newly born infant.

- Determined from auscultation over the apex with a stethoscope or direct palpation of cord or with stethoscope.
- Peripheral pulses are often difficult to feel.
- If no pulsation is felt on palpation of the cord do not assume there is no heart beat but auscultate the chest.

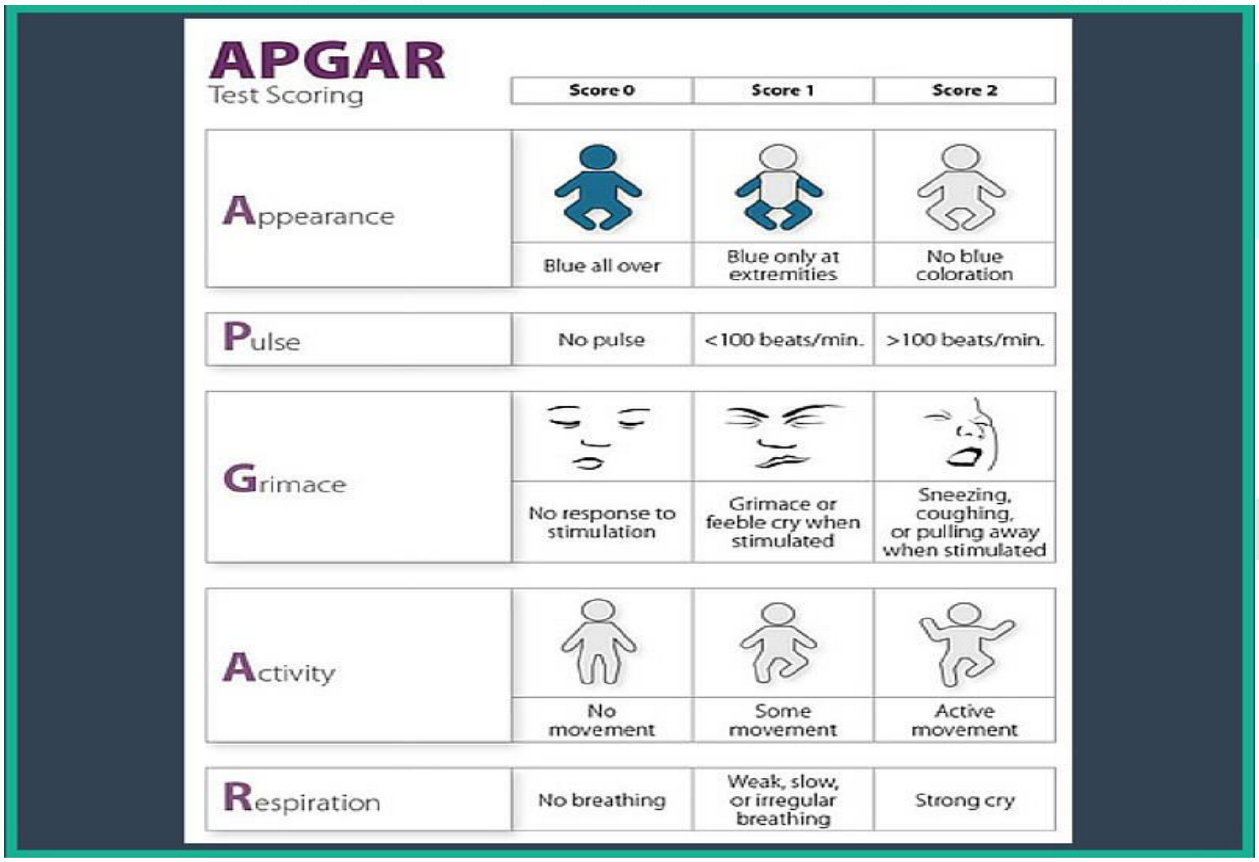
3.Colour

- Assessment of of colour is a poor proxy for oxygenation,therefore assessment of oxygenation can be aided by use of a pulse oximeter with neonatal probe attached to the infant's right hand.
- During labour the uncompromised infant has oxygen saturations of about 60% which after birth usually take 5-10 minutes to reach 90%.

- The well newly born infant should then be able to maintain a central pink colour in room air.
- Taking an Apgar score is not a prerequisite for resuscitation. The need for resuscitation must be recognized before the end of the first minute of life which is when the first Apgar score is taken.
- Apgar scoring has been used as a systematic tool to assess and document the clinical status of the newborn at birth (at 1 and 5 minutes of life).
- The newborn is examined for five signs: breathing, heart rate, muscle tone, reflex irritability and colour
- The score depends not only on the severity of birth asphyxia but also on other factors such as drugs given to the mother, anaesthetics, fetal infection, fetal anomalies and prematurity.

Initial Assessment: APGAR score

- Assesses neonatal well-being & resuscitation :
  1-min score ➡ to assess if the baby needs resuscitation
  5-minute score➡ to assess the efficacy of resuscitation and to diagnose HIE
- Each variable must be evaluated at 1 and 5 minutes.



APGAR Score 8-10

- Achieved by 90% of neonates
- Nothing is required, except :
  - nasal and oral suctioning
  - drying of the skin
  - maintenance of normal body temperature.

APGAR Score 5-7

"resuscitation "

- Respond to vigorous stimulation
- Oxygen blown over the face.

Apgar Score 3-4

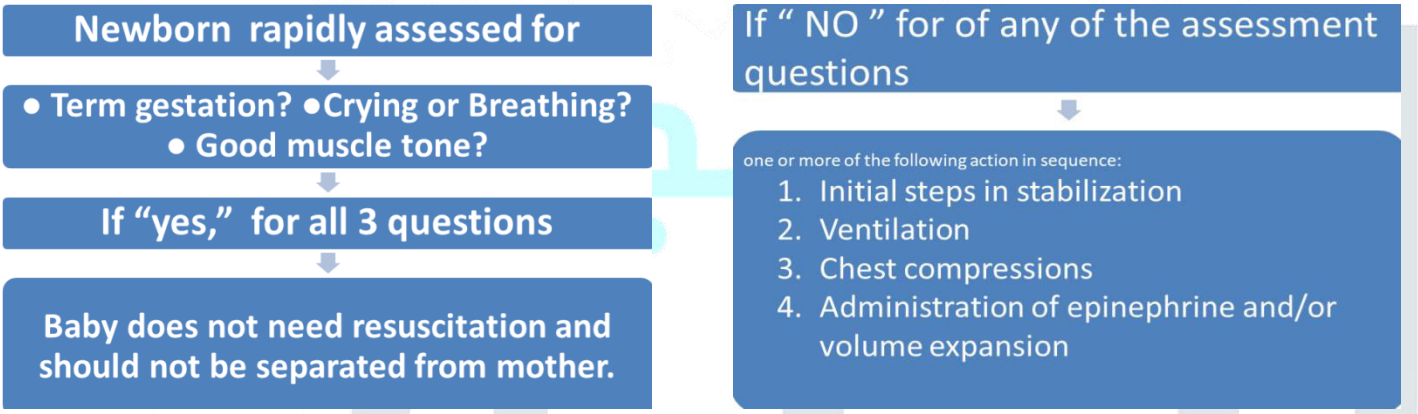
- These Neonates are moderately depressed at birth.
- They are usually cyanotic and have poor respiratory efforts.
- But they usually respond to BMV, breath, and become pink.

Apgar Score 0-2

These neonates severely asphyxiated and require immediate resuscitation.

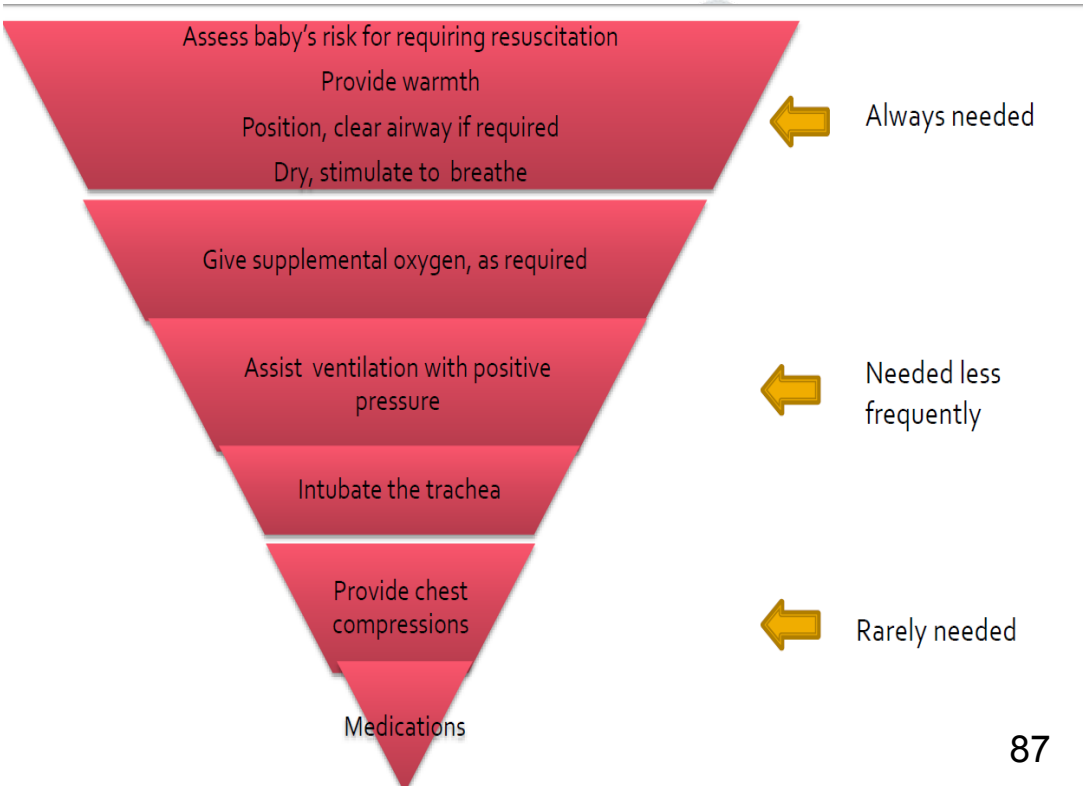
- intibation

Which babies need resuscitation?



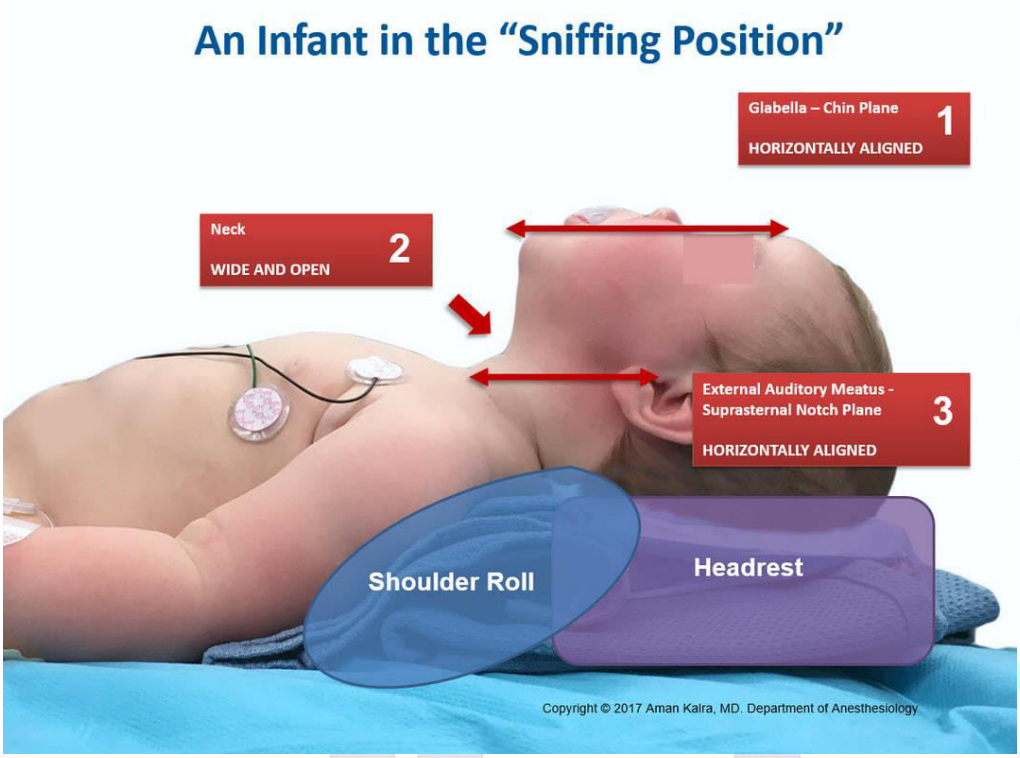
Resuscitation of neonates

- Resuscitation pyramids →



Steps of resuscitation

- **<u>The initial steps</u>** of newborn resuscitation are to **maintain normal temperature** of the infant, position the infant in a "sniffing" position to open the airway, **clear secretions** if needed with a bulb syringe or suction catheter, **dry the infant** which is the best tactile stimulation for breathing (unless preterm and covered in plastic wrap), and **stimulate the infant** to breathe.



Why babies have hypothermia?

- Neonates have a high ratio of skin surface area to body weight, which increases heat loss and **evaporative fluid loss**.
- **The fluid loss from the skin** (due not to sweating but to direct transdermal water loss) results in massive heat loss.
  - The thin fetal skin, with **blood vessels that are near the surface**, provides **poor insulation**, which leads to further heat loss.
  - The **low amount of musculature** and the **inability to shiver**.
  - A **lack** of thermal insulation, e.g., **subcutaneous fat and fine body hair** (especially in premature).
  - The **nervous system is not fully developed** and does not respond quickly and/or properly to cold (e.g., by vasoconstriction of skin blood vessels).
  - **Conduction and Evaporation mainly**

Thermoregulation

- ❖ Neonatal **hypothermia increases oxygen consumption** and metabolic demands, which can impair subsequent resuscitative efforts, especially in the asphyxiated or preterm infant.
- ❖ **During transition, the use of plastic wraps and the use of skin-to-skin contact reduce hypothermia.**
- ❖ It is recommended that the temperature of newly born nonasphyxiated infants be maintained between 36.5°C and 37.5°C after birth through admission and stabilization.
- To minimize heat loss, the delivered infant is first placed in a warmed towel or blanket. Raising the environmental (room) temperature to 26°C (78.8°F) will also help in reducing neonatal hypothermia.
- Maintain **Humidity** of 40-60% in full term infants
  60-100% in preterm infants.

ABC's of Resuscitation

A – Establish an open **Airway**

- Position infant
- Suction mouth then nose

B – initiate **Breathing**

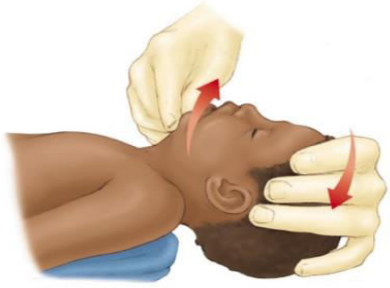
- Use tactile stimulation
- Use PPV if necessary

C – Maintain **Circulation**

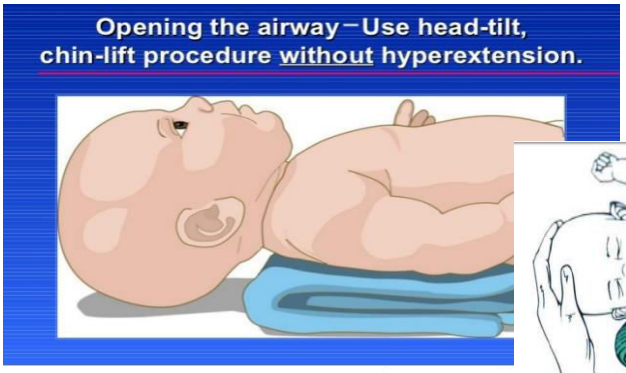
- Stimulate and maintain circulation
- Chest compressions
- Drugs

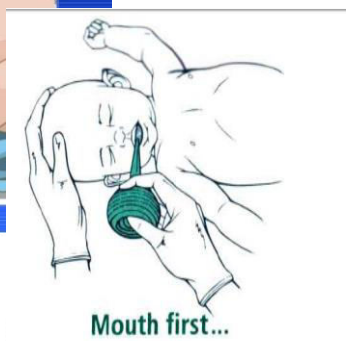
Airway management

- ❑ Position : The infant should be positioned so as to open the airway



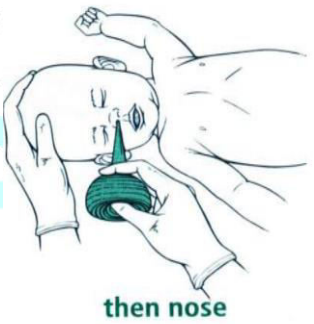
Head-Tilt/Chin Lift
maneuver in an infant.
Do not overextend the head & neck.

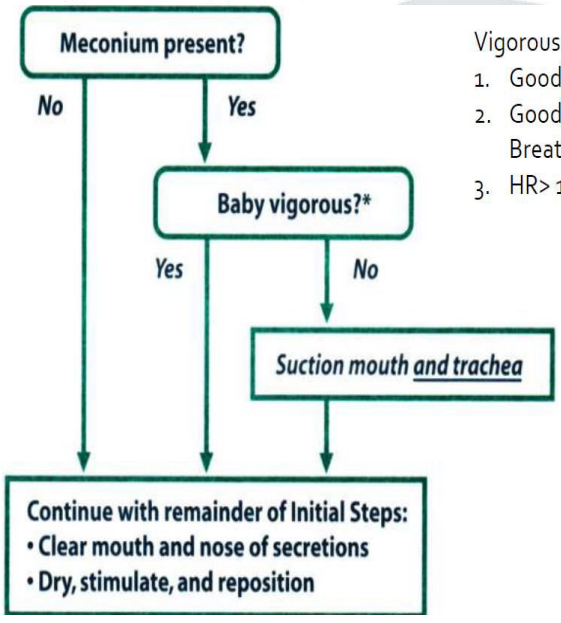




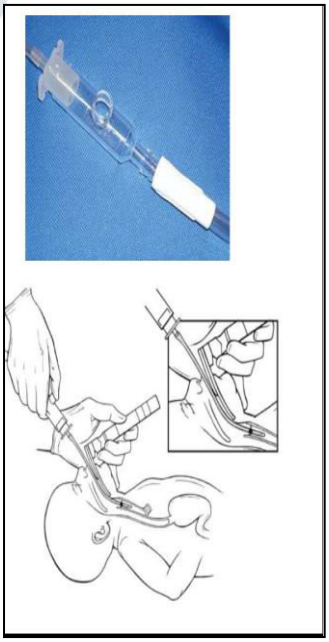
- ❑ Suction : The mouth and nose should be suctioned.

- **Mouth then nose** to prevent aspiration of mouth contents
- A bulb syringe should be used for the initial suctioning.
- Suction is done to : assess reflex and clean the airway





Vigorous if
1. Good tone
2. Good Cry/ Breathing
3. HR> 100/min



- ❑ Insert Laryngoscope.
- ❑ Clear the mouth and posterior pharynx using 12F/14F catheter.
- ❑ Insert ET tube.
- ❑ Attach ET tube to meconium aspirator and suction source.
- ❑ Apply suction and remove slowly.

- ❑ Remove ETT and visualize the vocal cord by a direct laryngoscope. Still meconium ? → Reinsert ETT and suction again

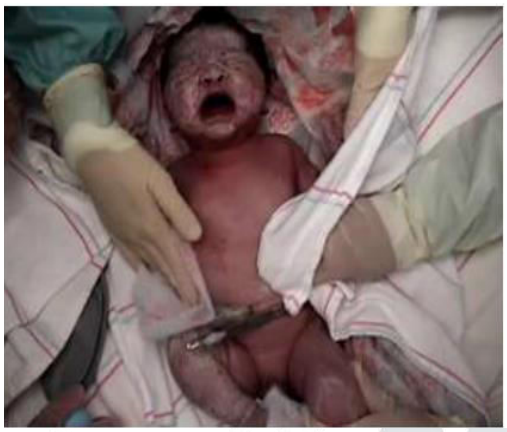
Still meconium ? ↩
if clear airway stimulate breathing

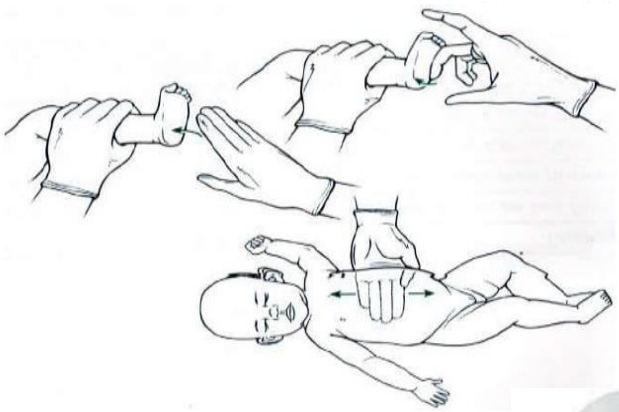
stimulation

Drying and suctioning often provide enough stimulation to initiate breathing; however, if more vigorous stimulation is necessary, **gently slapping the soles of the feet or rubbing the back may be effective.**

The back should be visualized briefly for any **obvious defect** in the spine before beginning these maneuvers.

- At this point, the infant's respiratory rate, heart rate, and color should be evaluated.

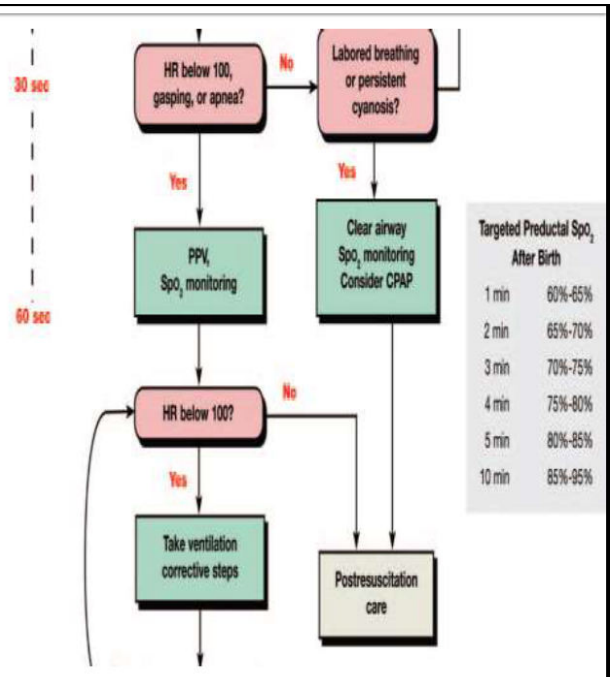




- Infants who have a sustained heart rate higher than 100 beats/min and adequate respiratory effort but who remain **cyanotic** should receive blow-by oxygen via oxygen tubing or a mask.
- Supplemental oxygen should be initially provided with a Fi o2 of 1 at a flow rate of 8-10 L/min.
- If oxygen is to needed for a long period, heated humidified oxygen should be supplied via an **oxygen hood**

If Apneic or HR < 100 bpm:

- Provide positive-pressure ventilation,spo2 monitoring.
- If breathing, and heart rate is >100 bpm but baby is cyanotic, give supplemental oxygen, spo2 monitoring. If cyanosis persists, provide positive-pressure ventilation
- If respiratory distress is persistent , consider CPAP and connect oximeter

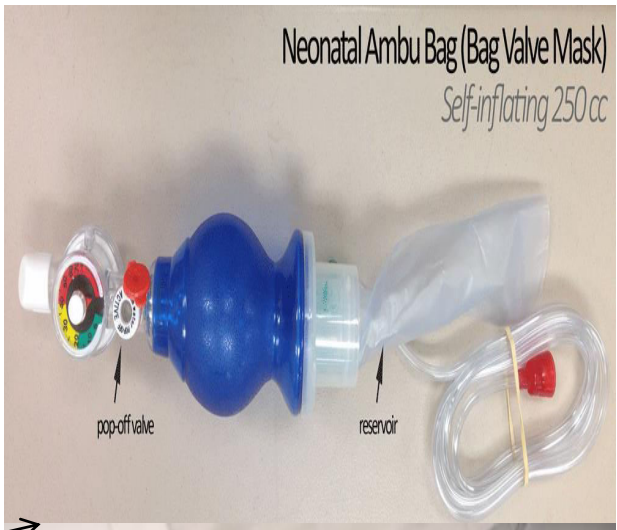


Positive pressure ventilation

- Infants with adequate respirations who are experiencing respiratory distress (**tachypnea, grunting, flaring, retracting, or persistent central cyanosis**) may benefit from ppv.
- If the infant is apneic, is making inadequate respiratory efforts (**gasping**), or has a heart rate lower than 100 beats/min, PPV should be initiated immediately.
- Infants who have continued central **cyanosis** despite supplemental oxygen should also receive PPV.

- **Peak inspiratory pressure (PIP) :** Pressure delivered with each breath, such as the pressure at the end of a squeeze of resuscitation bag or at the end of breath with a T – piece resuscitator
- **Positive end – expiratory pressure (PEEP) :** The gas pressure which remains in the system between breaths, such as during relaxation and before the next squeeze

- **Continuous positive airway pressure(CPAP) :** Same as PEEP, but used when the baby is breathing spontaneously and not receiving PPV. It is pressure in the system at the end of spontaneous breath when a mask is held tightly on baby's face but the bag is not being squeezed.
- **Rate:** The number of assisted breaths given per minute



- Ambu bag (self-inflating bag)
  Make sure the mask size is appropriate ; should cover the nose, mouth and chin , And the head in semi-flexed position .

1- Connect the ambu bag to the oxygen but high flow should be avoided it inc risk of **pneumothorax**
2- An initial peak inflation pressure (pip) of 20 cm H2O is effective, but 30-40 cm H_2O may be required in some term babies
3- If pressure is not being monitored, the minimal inflation required to achieve ↑ in HR should be used
4- Respiratory rate 40-60 breaths/min to promptly achieve or maintain >HR 100/min
5- Positive end expiratory pressure (peep) should be 5-7 cm H_2O (to keep the alveoli open)
6- Fio2 is 21-100 %

- Contraindications of Ambu bag : thick meconium and diaphragmatic hernia

CPAP

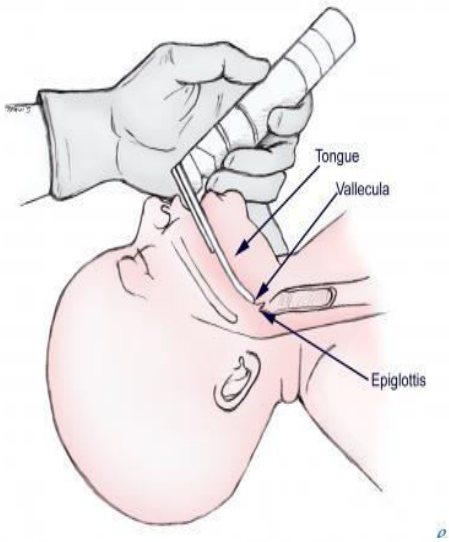
- Recommended in **preterm newborn who are breathing spontaneously**, but with difficulty.
- Starting infants on CPAP, **↓ the rates of intubation and Mechanical ventilation , surfactant use, and duration of ventilation**, but **↑ rate of pneumothorax.**

Intubation :

INDICATIONS :

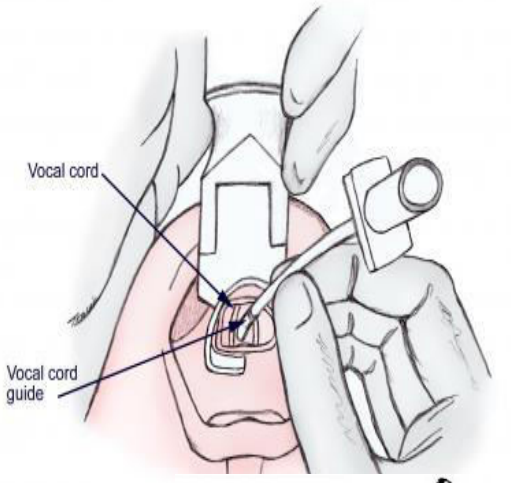
- Initial endotracheal suctioning of non vigorous meconium stained newborns.
- If BMV is ineffective or prolonged (Intractable Apnea)
- Newborns born without a detectable HR
- Apgar score <3
- PH < 7.3 , PaO2 <50 mmHg , PaCO2 <55 mmHg
- Expected need for continued or prolonged ventilation

- For special resuscitation circumstances, such as CDH and ELBW.



1- The head should be semi flexed
2- Hold the laryngoscope in the left hand, and stabilize the infant's head with the right hand.
3- Slide the laryngoscope blade over the tongue and gently compress forward on the tongue
4- Then upward and forward without touching the upper lip
5- Visualize the vocal cords
6- Maintain direct visualization of the vocal cords as you place the endotracheal tube with your right hand

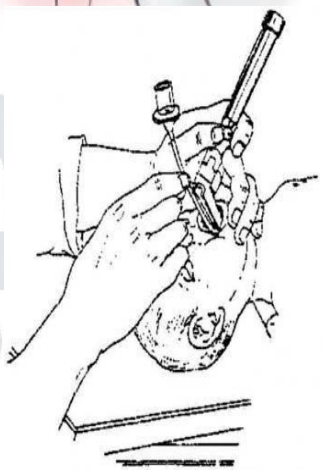
   - If the vocal cords are approximated, wait for them to open.
   - Do not force the endotracheal tube through closed vocal cords; doing so can damage the cords.



7- Stabilize the endotracheal tube in position
8- remove the laryngoscope blade

Ideally, the entire process of tracheal intubation should take less than 20 seconds

After intubation if the baby is still <u>not</u> improving :



. Check the tube placement by direct visualization with the laryngoscope
. The tube could be in the right side
. Transillumination test for pneumothorax
. Check the tube for a mucous or blood plug
. Palpate the anterior fontanelle (hemorrhage)
. Prompt ↑ HR is the best indicator that the tube is in the tracheobronchial tree and providing effective ventilation.
. Exhaled CO2 detection is the recommended method of confirmation of ETT placement.
. Poor or absent pulmonary blood flow may give false-negative results (ie, no CO_2 detected despite ETT in the trachea).
. The best thing to confirm its position is direct laryngoscopy

- **Other clinical indicators of correct endotracheal tube placement are :**
  - Condensation or mist in the ETTالتكثيف أو الضباب
  - Chest movement
  - Presence of equal breath sounds bilaterally
  - Improvement in skin color and SpO2

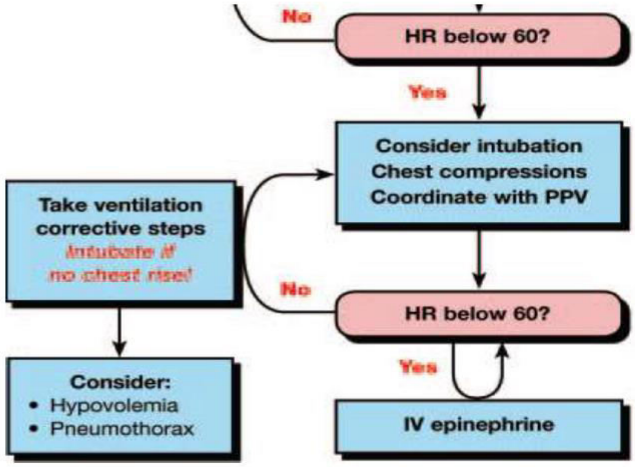
– Patient not crying

- Because the chest is small, breath sounds are well transmitted within the thorax.
- A difference in breath sounds between the two sides of chest should raise suspicion of pneumothorax, atelectasis, or a congenital anomaly of the lung.
- Presence of loud breath sounds over the stomach suggest Tracheoesophageal Fistula.
- Failure to adequately ventilate the lungs at birth may make hypoxemia worse and lead to CNS damage or even death.
- If the PaO2 > 70-80 mm Hg or SaO2 >94%, FiO_2 (if higher FiO2 is used) should be reduced untill SaO2 and PaO2 are normal for age. (normal SaO2 ≈87-95%, which is associated with a PaO2 of 55-70 mm Hg)
- Retinopathy of prematurity can occur in premature neonates(<34 wks gestation) with a PaO2 of ≈150 mm Hg for 2-4 hrs.

Chest compression

Indications :

- HR <60/min despite at least 30 sec of effective PPV



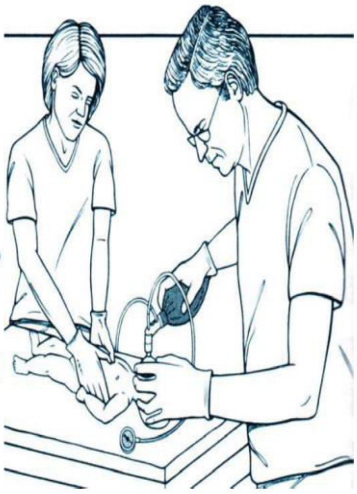
➢ **Strongly consider Endotracheal intubation at this point as it ensures adequate ventilation and facilitates the coordination of ventilation and chest compressions**

Rationale:

- HR<60/min despite PPV indicates very low O2 levels and significant acidosis → depressed myocardium → no blood in lungs to get oxygenated(supplied by PPV)
- Chest compressions + effective ventilation (ET/PPV) → oxygenation of blood → recovery of myocardium to function spontaneously → HR increases → O2 supply to brain increases

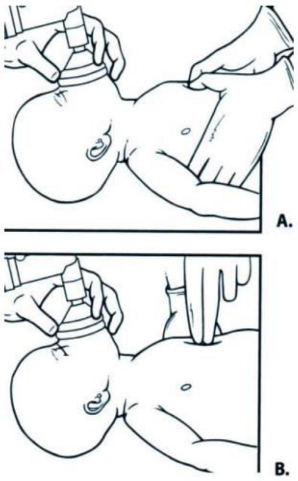
Positions :

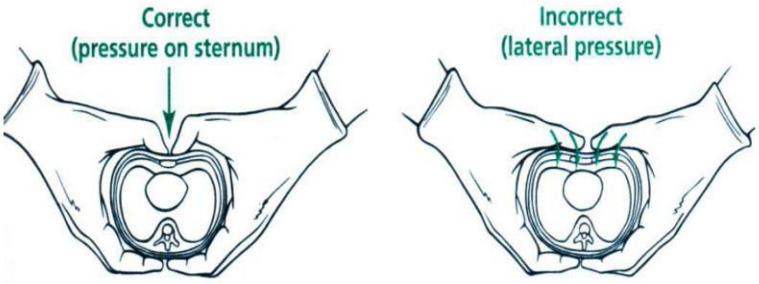
- Chest compressions are of **little value unless** the lungs are effectively **ventilated**
- 2 persons are required
  - 1 – chest compressions provider should have access to the chest with his hands positioned correctly
  - 2 – Ventilation provider should be at head end to maintain effective mask-face seal or to stabilize ET tube



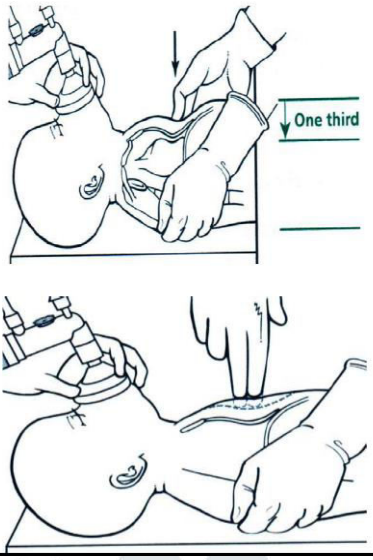
Technique:

- **Thumb technique:** 2 thumbs depress the sternum, hands encircle the torso and the fingers support the spine. **Preferred** technique
- **2 – Finger technique:** Tips of middle & index/ring finger of one hand compresses sternum, other hand supports the back.





- Depth : 1/3rd of the anteroposterior diameter of chest.
- Duration of downward stroke should be shorter than the duration of release
- Do not lift the fingers off the chest



When to stop chest compressions?

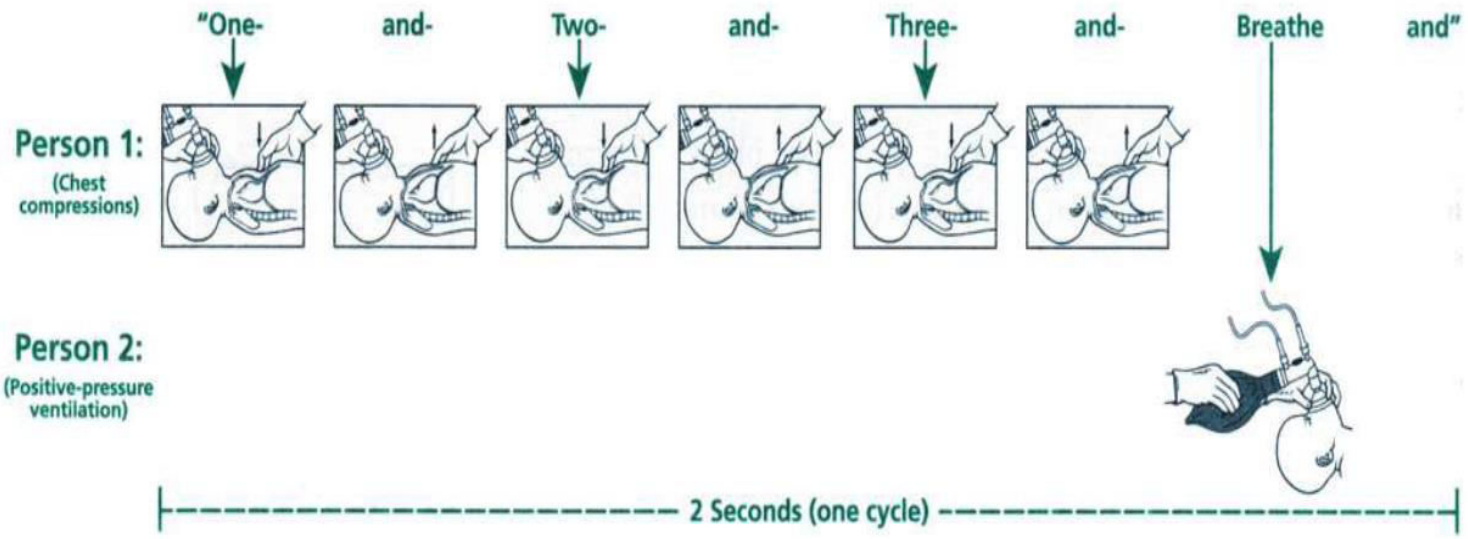
- Reassess after 45-60 sec, if HR > 60/min stop chest compressions and increase breaths to 40-60 per minute.

If HR is not improving...

- Insert an umbilical catheter and give IV epinephrine

Complications:

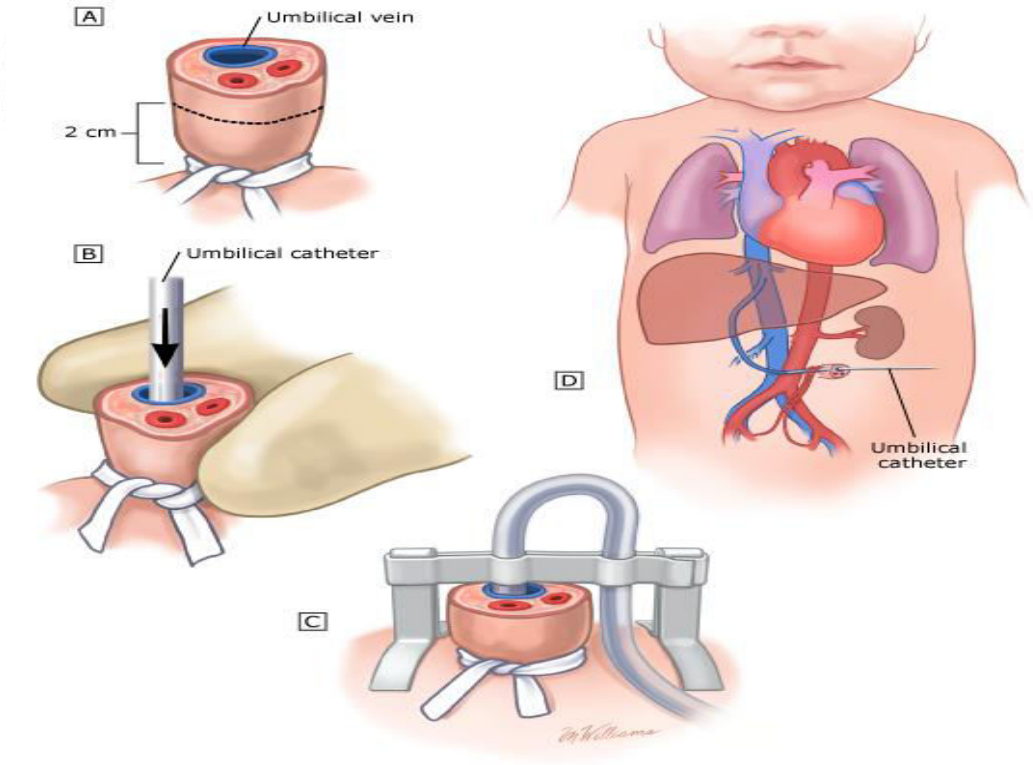
- Laceration of liver
- Breakage of ribs

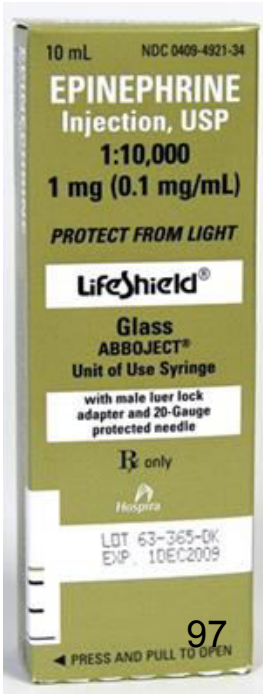


- **RESUSCITATION DRUGS**

- if the HR remains < 60/min despite one minute of adequate ventilation and chest compressions with 100% O_2 ,adrenaline or volume expansion or both are indicated

Route	Considerations[1]
Umbilical vein	• The umbilical vein is the most rapidly accessible intravascular route for Adrenaline and an umbilical venous catheter (UVC) can also be used for fluid administration • A 3-way tap should be attached to the UVC and both primed with normal saline before use • A UVC can provide continued vascular access until an alternative route is established • Blood gases from the UVC may be useful in guiding treatment
Endotracheal tube	• Give only Adrenaline via the ETT: o ETT administration of Adrenaline is acceptable when the heart rate is less than 60 bpm despite adequate ventilation and chest compressions and when there is no intravenous (IV) access[1] o Administration of ETT Adrenaline should not delay attempts to obtain vascular access for administration of IV Adrenaline
Peripheral vein	• Access can be difficult • Access may take too long
Intraosseous lines	• Not commonly used in newborns • Can be used if umbilical or venous access is not available • Consider if the resuscitator has greater experience with inserting intraosseous lines





- IV is the preferred route: UVC is preferable to intraosseous
- Recommended IV dose is 0.01-0.03 mg/kg/dose; rapid bolus
- followed by 1ml of 0.9% NS flush
- Intratracheal dose is higher (0.05 to 0.1 mg/kg); 1:10,000 (0.1 mg/mL); may be considered while IV access is being obtained; Follow with PPV

- **Can be repeated every 5 minutes, if HR remains < 60/min.**

If there is no response to administration of epinephrine, the clinician should reassess the earlier resuscitative steps to ensure that they have been performed correctly. If resuscitative efforts were completed correctly, then another problem such as hypovolemia might be present

Volume Expansion

Detection of Hypovolemia:

- measuring the arterial BP and
- by physical examination (i.e. pale skin color, have poor capillary refill time, poor skin perfusion, extremities are cold, and pulses (radial and posterior tibial) are weak or absent, and temperature.

- CVP measurements are helpful in detecting hypovolemia and in determining the adequacy of fluid replacement.
- Normal CVP in neonates is 2-8 cm H_2O.

Treatment of Hypovolemia

- Best be done with blood and crystalloids
- If hypovolemia is suspected at birth, Rh-negative type O PRBCs should be available in delivery room before neonate is born.
- Crystalloid and blood should be titrated in 10 mL/kg and given slowly over 10 minutes.
- At times, >50% of the blood volume (85 mL/kg in term; and 100 mL/kg in preterm) must be replaced, especially when the placenta is transected or abrupted.
- In most cases, <10-20 mL/kg of volume restores mean arterial pressure to normal.
- Care should be taken to avoid giving volume expanders rapidly, leading to hypertension and Intra ventricular H.
  Hypertension may disrupt the intracerebral vessels and cause intracranial hemorrhage if cerebrovascular autoregulation is absent.

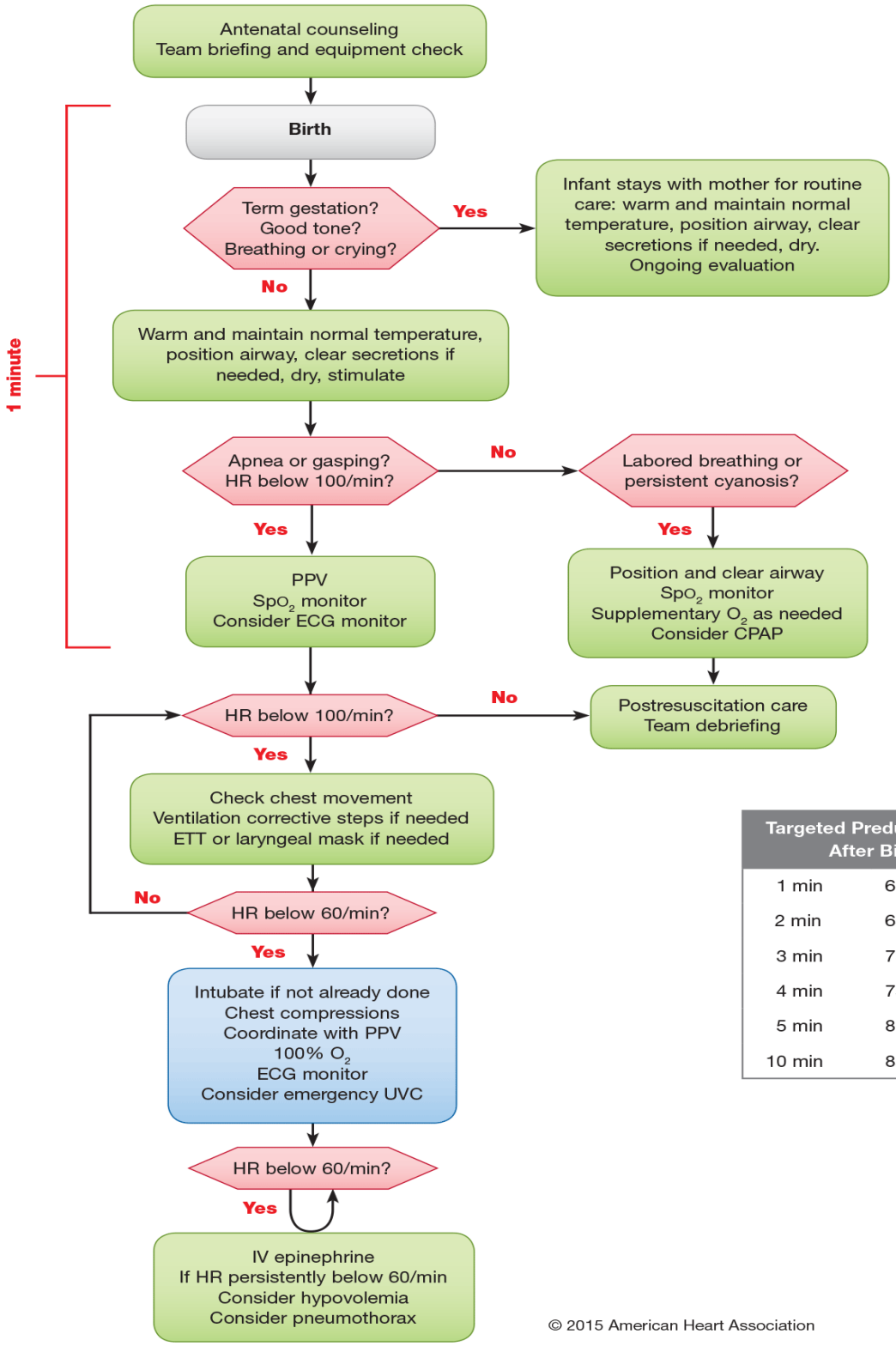
Postresuscitation Care

- Babies who require resuscitation are at **risk for deterioration** after their vital signs have returned to normal.
- The infant should be maintained in, or transferred to an environment where **close monitoring** can be provided.

Monitoring required may include:

- Oxygen saturation(SpO2)
- Heart rate and ECG
- Respiratory rate and pattern
- Blood glucose measurement
- Blood gas analysis
- Fluid balance and nutrition
- Blood pressure - Temperature - Neurological

Neonatal Resuscitation Algorithm—2015 Update



Targeted Preductal SpO_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%

Naloxone —indicated if the mothers suspected of using or has received narcotics it should be avoided if the mother has a history of long term opoide abuse bec of the risk of precipitating acute

withdrawal ,seizure and death

Sodium bicarbonate — indicated if sever metabolic acidosis is present , initial dose is 2 mEg/kg

Glucose – in case of hypoglycemia : hypoglycemia is treated with an infusion of 10% solution of IV glucose infusion dose of 2-3ml/kg followed by a continues infusion.

Neonatal Infections Part II

Viral Infections in the Neonate

Vertically Transmitted Viral Infections in the Neonate :

- Herpes Simplex Virus (HSV)
- Varicella Zoster Virus (VZV)
- Hepatitis B
- Cytomegalovirus (CMV)

- **Herpes simplex virus (HSV)**
  - Herpes simplex virus (HSV) has been associated with neonatal disease for more than 6 decades.
  - Over the past 20 years, there have been major advances in our knowledge of the epidemiology, pathogenesis and natural history of this disease. In addition, the availability of effective antiviral therapy has resulted in major advances in the management of neonatal HSV infections.
  - Despite these advances, HSV remains a major cause of morbidity and mortality among neonates.

. **Epidemiology**

Incidence of neonatal infection:

- Data from the Canadian Paediatric Surveillance Program (CPSP) indicate that, between 2000-2003, there were 43 cases of neonatal HSV (5.9 per 100,000 live births in Canada) and a case fatality rate of 15.5%.
- While the incidence varies across regions in the USA, a rate of 1 in 3200 deliveries was recently documented.
- approximately 70% of neonatal disease is caused by HSV type 2 and 30% by HSV type 1.

. **Herpes Simplex Virus (HSV)**

- Large, enveloped DNA virus
- HSV type II (usually genital)
- HSV type I (usually facial and oral)
- Either type can exist at either location
- Transmission to the neonate occurs via the birth canal or by ascending infection
- Postnatal transmission can occur

. **Routes of Transmission**

- 85% via infected maternal genital tract
- Ascending infection , or when pass through the birth canal .
- 10% postpartum
- 5% (or less) – intrauterine/congenital infection
- HSV2 = 70-75%, HSV1 = 25-30%

- **(HSV)**

Postnatal Transmission

- Mother or father with non-genital infection :
  hands, mouth, nipple

- Nosocomial spread from infected infant to non-infected infant :
  usually via the hands of nursery personnel

- **Risk of Neonatal Infection**
  - Primary maternal infection
    Risk of transmission to infant 33-50%

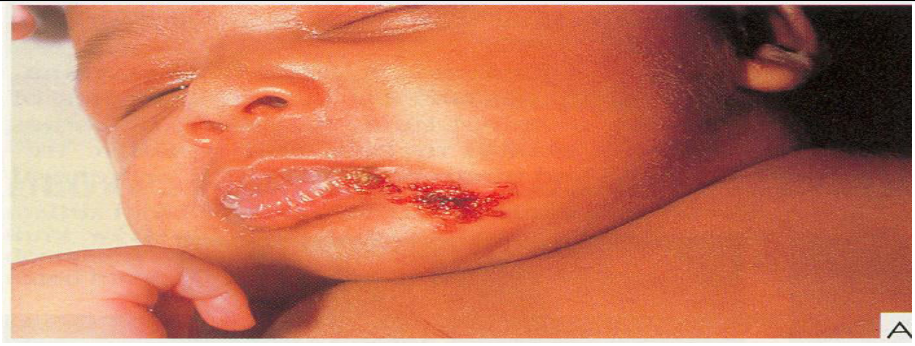
  - Recurrent maternal infection
    Risk of transmission to infant 3-5%

  - Relative risk varies:
    Vaginal delivery vs. Cesarean section
    Length of time membranes ruptured >6hr
    Also At Risk: Premature, Fetal scalp monitoring

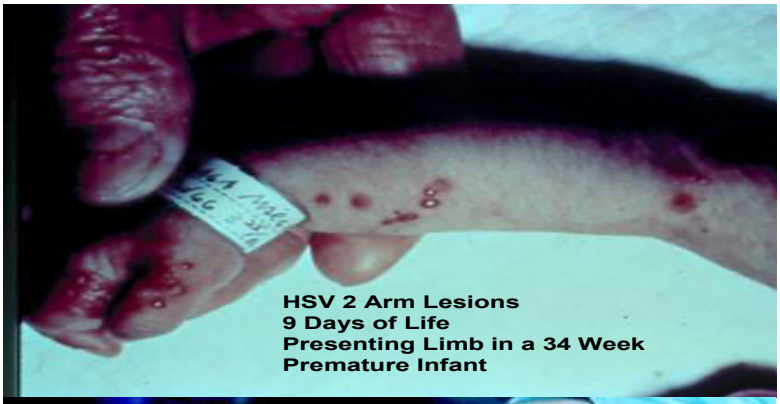
- **Clinical Manifestations of Neonatal Disease**
  - **Symptoms usually occur from birth to two weeks but can occur as late as 4-6 weeks**
  - **Three clinical syndromes:**
    - Multiple organ, systemic Disseminated infection
    - Localized central nervous system disease
    - Localized infection to skin, eyes (conjunctivitis, keratitis, chorioretinitis), ,mouth (SEM) and the presenting part .

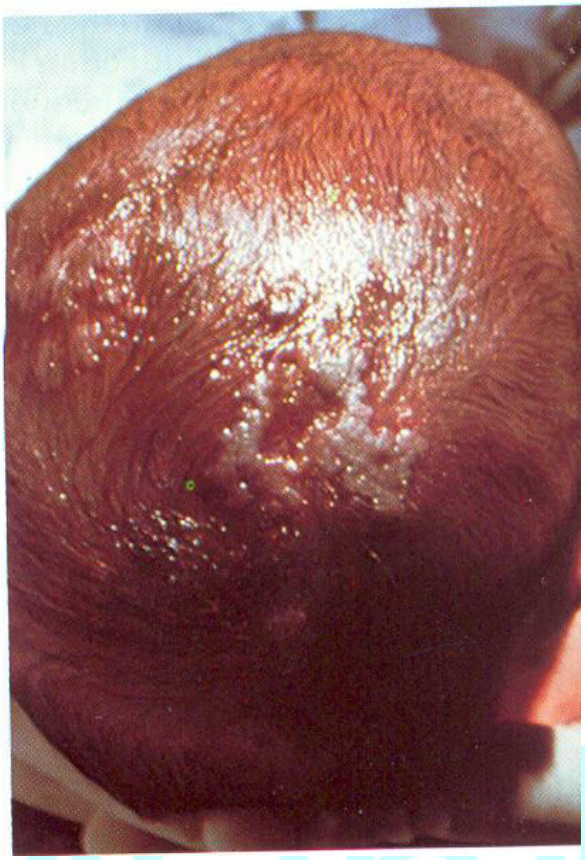
- **Skin Lesions**
  - Vesicles may have already ruptured and may look more like impetigo or mild cellulitis
  - Usually at presenting part of baby or site of instrumentation
  - 1/3 of infants with systemic disease will lack skin lesions
  - Another 1/3 will manifest skin lesions AFTER onset of systemic disease

- **Skin, Eye, Mouth (SEM)**
  - Approximately ½ of all HSV infections
  - 1st-2nd week presentation
  - Limited to skin, eye, mouth/mucous membranes
  - 60-70% of untreated patients progress to CNS/disseminated disease
  - Long term neurologic sequelae seen in 30% of cases – even if treated

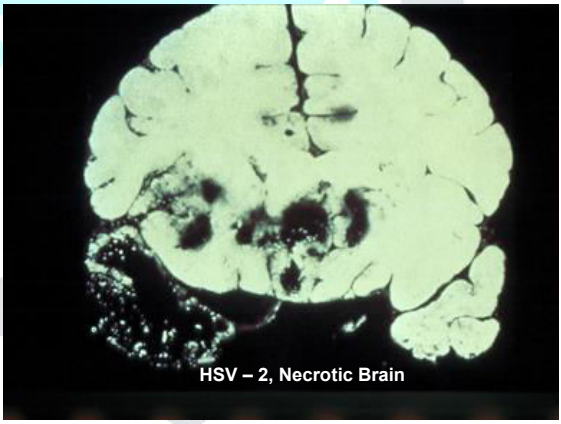


"Presenting Part" (SEM)





- **HSV - CNS Disease**
  - Encephalitis, mainly involving the temporal lobes
  - Early to 3rd week of life presentation
  - Skin lesions may appear late
  - 35% of all cases, only 2-5% untreated survive normally

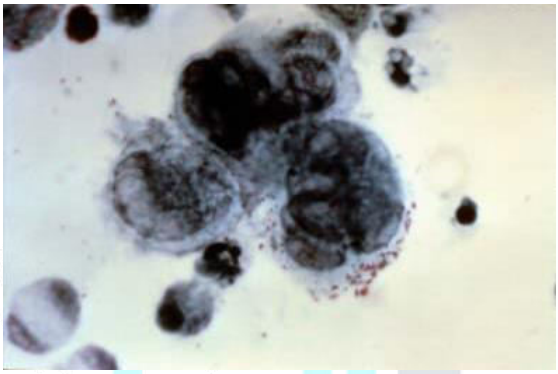


- **Symptoms of Systemic Disease**
  - **Appearance of sepsis:**
    - Fever, lethargy, poor feeding
    - Must rule out bacterial infection as well
  - **Respiratory distress**
  - **Seizures:**
    - Tend to be recurrent and difficult to control
    - Spinal fluid shows elevated white blood cells (mostly lymphocytes), erythrocytes, and protein , low glucose (mimic bacterial infection) + PCR

- **Mortality and Morbidity**
  - **Isolated skin, eye, or oral disease (20%)**
    - 25% of infants will develop neurologic abnormalities despite lack of symptoms at presentation
  - **Central nervous system CNS disease (33%)**
    - 17-50% mortality
    - 40% of survivors will have neurologic sequelae
    - microcephaly, spasticity, paralysis, seizures, deafness, blindness

- **Disseminated Disease**
  - **Without antiviral therapy:**
    - 80% mortality
    - Most, if not all, survivors will have permanent neurologic sequelae
  - **With antiviral therapy:**
    - 15-20% mortality
    - 40-55% of survivors will have permanent neurologic sequelae

- **Laboratory Diagnosis**
  - Tzanck smear
  - Serology
  - Viral cultures
  - Polymerase chain reaction



  - **Tzanck Smear** ⟶
    - ☒ Scraping from base of vesicle
    - ☒ Positive slides will show multinucleated giant cells
    - ☒ Quick screen but only 75% sensitive

  - **Serology**
    - ☒ will demonstrate rising HSV antibody titers
    - ☒ These rises occur late in the course of disease and are not particularly useful in making treatment decisions
    - ☒ Recurrent infections in mother often do not produce a rise in titers

  - **Viral Culture**
    - ☒ Still the gold standard
    - ☒ Viral detection usually positive within 1-3 days of inoculation
    - ☒ Viral cultures from the conjunctiva, naso-pharynx, mouth, stool, and urine at 24-48 hours of life
    - ☒ Cultures sooner if symptomatic
    - ☒ All of the above plus cultures of any skin lesions and the spinal fluid
    - ☒ Always obtain cultures prior to starting empiric acyclovir
    - ☒ in patients with localized CNS disease, CSF cultures are usually negative. so , polymerase chain reaction (PCR) is an important diagnostic test as it is more sensitive than culture.

  - **Polymerase Chain Reaction**
    - ☒ available
    - ☒ Relies on amplification of native HSV DNA…..
    - ☒ Primary limitations include cost and possibility of false positives
    - ☒ PCR sensitivity rates vary from 75% to 100%

  - **Acyclovir**
    - ☒ Minimum effective dose in neonates is 30 mg/kg/day in three divided doses
      - Most experts recommend higher doses: 45 to 60 mg/kg/day
    - ☒ Neonatal HSV should be treated with parenteral acyclovir rather than oral therapy
    - ☒ Minimum length of therapy is 14 days
      - 21 day course may prove more effective

- **Special Considerations**
  - **Intravenous acyclovir:**
    - Ensure adequate hydration to prevent precipitation of drug in kidneys
    - Infuse drug over one hour
    - The use of higher doses of acyclovir is associated with an increased frequency of neutropenia
  - **Ocular disease:**
    - Topical therapy with 1-2% trifluridine, 1% iododeoxyuridine, or 3% vidarabine
    - Requires acyclovir as well

- **Recurrent Skin Lesions**
  - Common in surviving infants
  - Greater than three recurrences in the first 6 months of life correlates with adverse neurologic and/or ocular sequelae
  - Role of prophylactic oral acyclovir not yet clear
  - Prolonged oral acyclovir associated with neutropenia

- **Recommended Obstetric Management**
  - All women in labor should be questioned regarding a history of HSV in themselves or sexual partners
  - During the physical exam care should be taken to look for genital and non-genital lesions
  - If Cesarean section is to be performed, it is best done within 4-6 hours of membrane rupture
  - Scalp monitors and scalp sampling should be avoided
  - Primary and Recurrent genital HSV during pregnancy : give suppressive acyclovir therapy starting at 36 weeks' gestation at a dose of 400 mg tid

- **Preterm Infants**
  - **When a woman presents in**
    - preterm labor
    - active HSV lesions,
    - AND ruptured membranes

    the course is not clear:

  - **Options include:**
    - Allow labor to progress (consider acyclovir for mother)
    - Delay delivery and give steroids for lung maturation, some experts recommend that intravenous acyclovir (15 mg/kg per day in 3 divided doses, maximum 1200 mg/day) be given to the mother if labor and delivery are delayed
    - Immediate Cesarean section

- **Vaginal Delivery Over a Primary Genital Infection**
  - 33-50% risk of infection in the newborn
  - Risk is higher if :
    - premature
    - instrumentation during delivery, or if lacerations occur
  - Most experts recommend empiric acyclovir treatment at birth
  - Obtain viral cultures prior to starting therapy

- **Vaginal Delivery Over a Recurrent Genital Lesion**
  - Risk of neonatal infection 5% or less
  - No emperic therapy required
  - Surveillance cultures at 24- 48 hours
  - Careful examination for vesicles and systemic signs of infection
- **Delivery by Cesarean Section with Active Maternal HSV**
  - Obtain surveillance cultures at 24-48 hours of life
  - Empiric therapy not recommended
    - Consider therapy if primary lesion and membranes ruptured greater than 6 hours prior to delivery
    - if culture results from the infants are positive for HSV or if HSV infection is strongly suspected on clinical grounds
- **Maternal History of HSV (*No Active Lesions)***
  - Not an indication for Cesarean section
  - No special isolation required for infant
  - Routine viral cultures not necessary
- **General Recommendations**
  - Infants exposed to active lesions should be isolated from other infants in nursery
  - Parents should be instructed in strict hand washing techniques
  - Parents with cold sores should not kiss infants until lesions healed
  - Other non-genital herpetic lesions should be covered
- **General Considerations**
  - Breast feeding is NOT contraindicated unless there are lesions on the breast
  - Elective circumcisions should be delayed at least one month in high risk infants
    Infection can manifest as late as 6 WEEKS!

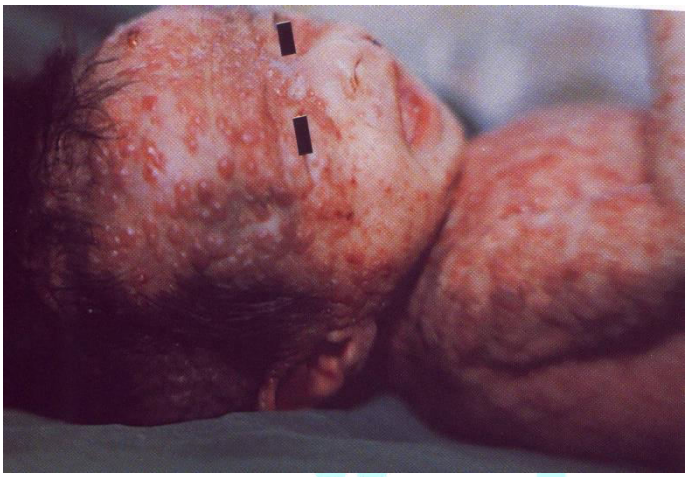
(VZV) Varicella Zoster Virus

- Causes chicken pox and shingles
- Humans are the *only known reservoir*
- *Highly contagious*
- Transmission is by contact or airborne droplets

- **Epidemiology**
  - Exposure to a household results in infection in virtually all susceptible members
  - Incubation period usually 14-16 days
    - Can range 10-21 days
  - Patients are contagious from 5 days prior to and 2 days after the onset of the rash
    - Immunocompromised patients contagious for duration of rash
- **Congenital Varicella**
  - Caused by maternal infection in the 1st trimester to early 2nd trimester
    - Greatest risk between 13-20 weeks gestation
  - Limb atrophy and scarring
  - Chronic encephalopathy and cortical atrophy
  - Chorioretinitis, micropthalmia, cataracts

- **Neonatal Varicella**
  - Transplacental exposure
  - At risk when mother develops varicella from 5 days prior to 2 days after delivery
  - Can manifest from 1-16 days after delivery
  - High risk for disseminated varicella
    - Mortality rates as high as 30%
    - Prognosis much better if lesions develop greater than 5 days after delivery

Neonatal varicella :



- **Nosocomial Transmission**
  - Well documented in pediatric wards
  - Rare in newborn nurseries
  - High risk infants:
    - Premature infants (> 28 weeks gestation and > 1000 grams) whose mother has no history of varicella
    - Premature infants (< 28 weeks gestation or < 1000 grams) regardless of maternal history

- **Varicella Zoster Immune Globulin (*VZIG*)**
  - Provides passive immunity
  - Not effective once active disease occurs
  - Dosage: 125 units/10 kg
    - Minimum dose: 125 units
    - Maximum dose: 625 units
  - Never administer intravenously
  - Best given within 96 hours of exposure

- **Indications for VZIG (assuming significant exposure)**
  - Susceptible pregnant women
  - Newborn with onset of maternal varicella within 5 days prior through 2 days following delivery
  - Hospitalized premature > 28 weeks gestation and no maternal history of varicella
  - Hospitalized premature < 28 weeks gestation or < 1000 grams regardless of maternal history

- **VZIG**
  - Term infants exposed after 2 days of life are not at increased risk
    - VZIG not indicated
  - All infants who receive VZIG should be in strict isolation
    - 50% of infants still develop varicella though disease tends to be milder
      VZIG may prolong incubation as long as 28 days

(HBV)

- **HBV is a DNA hepadenavirus**
- **The virus can be isolated from:**
  - blood
  - wound exudate
  - semen
  - cervical secretions
  - saliva
- **It is not transmitted via the fecal oral route**

- **Serology**
  - **HBsAg** : (surface antigen)
    - Detection of acutely or chronically infected patients
  - **Anti-HBs** : (antibody to HbsAg)
    - Patients with immunity following : infection , or vaccination
  - **HBeAg :** ('e' antigen)
    - Patients at increased risk for transmitting HBV
  - **Anti-HBe :** (antibody to HBe)
    - Low risk for transmitting HBV
  - **Anti-HBc :** (Antibody to core antigen, HBcAg)
    - Evidence of acute or past infection
    - *Not present after immunization*
  - **IgM Anti-HBc:** (IgM antibody to HBcAg)
    - Acute or recent HBV infection

- **Risk to Newborn**
  - *Chronic HBV infection* occurs in 70-90% of infants delivered to mothers who are HBeAg positive
  - Those who escape perinatal infection remain at high risk for horizontal transmission during the first 5 years

- **Chronic HBV Infection**
  - High risk of acquiring :
    - chronic active hepatitis
    - cirrhosis
    - primary hepatocellular carcinoma
  - The risk of chronic infection is inversely proportional to the age at time of infection
  - Asymptomatic HBV carriers coinfected with the Hepatitis D virus can develop fulminant liver disease

- **Hepatitis B Immune Globulin**
  - Reserved for post exposure prophylaxis
  - Prepared from human donors with high anti-HBs titers
  - Standard Immune Globulin (IVIG) ineffective

- **Hepatitis B Vaccine**
  - Two commercial preparations available in the United States
    - Both products of recombinant DNA technology
  - The current vaccines produce an antibody response (after 3 doses) in > 90% of adults and > 95% of infants and children

- **Routine HBV Vaccination**
  - First dose at 0-2 months of age
  - Minimal interval between 1st and 2nd dose is one month
  - Minimal interval between 2nd and 3rd dose is two months
  - Minimal interval between 1st and 3rd dose is four months
  - When 1st dose is given between 0-2 months, give 3rd dose after 6 months

- **Infants of HBsAg + Mothers**
  - HBIG 0.5 ml IM
  - Hepatitis B Vaccine 0.5 ml IM
    - Both should be given within 12 hours of birth
    - inject at different sites
  - No contraindication to breast feeding

- ***Unknown* Maternal Status**
  - Obtain maternal blood for HBV serology
  - Administer HBV vaccine while awaiting results
  - If mother determined to be HBsAg +, then give HBIG as previously recommended
    - Dose should be given as soon as possible after results known and within 7 days of birth

- **Follow Up**
  - Vaccinate at 0, 1, and 6 months
  - Infants given their first vaccine at < 2 kg, should be given a 4th dose

Cytomegalovirus (CMV)

- **DNA herpes virus**
- **1% of all newborns have CMV infection at birth and are excreting virus**
- **Virus is transmitted both vertically and horizontally**

- **Modes of Transmission**
  - Transplacental
  - Via birth canal
  - Contact with infected urine or saliva
  - Blood transfusions and organ transplants
  - Breast milk
    - Most infants infected this way do not manifest clinical illness

- **High Risk Infants**
  - Severe disease in ~5% of in utero infections
  - Primary maternal infection at highest risk :
    - 10-20% will have mental retardation or hearing loss
    - Fetal risks greatest in first half of pregnancy
  - Premature infants
  - Immunosuppressed patients

- **Clinical Disease**
  - Most infants are asymptomatic
  - Mild to moderate disease:
    - Petechiae
    - Hepatosplenomegaly
    - jaundice
    - intrauterine growth retardation
  - Severe (Cytomegalic Inclusion Disease)
    The above findings plus:
    - Microcephaly
    - brain damage,
    - cerebral calcifications
    - chorioretinitis

- **Diagnosis**
  - Virus can be cultured from urine, pharyngeal cultures, leukocytes, human milk, semen, and cervical secretions, tissue and other body fluids
  - Fourfold antibody titer rise
  - Polymerase chain reaction
    - Proof of congenital infection requires cultures or serology within three weeks of birth

- **Treatment**
  - Gancyclovir
    - Beneficial in treating retinitis
    - Limited data on congenital infections though potentially helpful
  - CMV Immune Globulin
  - Vaccine is currently experimental

- **Prevention**
  - STRICT HAND WASHING by hospital personnel
  - Use only CMV negative blood in premies and immune suppressed patients
  - Human Milk
    - Donor milk should be frozen or pasteurized

Hydrocephalous

Definition :
Hydrocephalus is not a specific disease; it represents a diverse group of conditions that result from impaired circulation and/or absorption of CSF or, in rare circumstances, from increased production of CSF by a choroid plexus papilloma.

There is abnormal enlargement of cerebral ventricles and/or subarachnoid space as a result of excess cerebrospinal fluid (CSF) accumulation.

- The incidence of congenital hydrocephalus is 3 per 1,000 live births in US .
- The incidence of acquired hydrocephalus is not known exactly due to the variety of disorders that may cause it.

Physiology:
Production of csf by :

- Choroid plexus in the ventricular system(75%).
- extrachoroidal sources, including the capillary endothelium within the brain parenchyma(25%).

control of production:

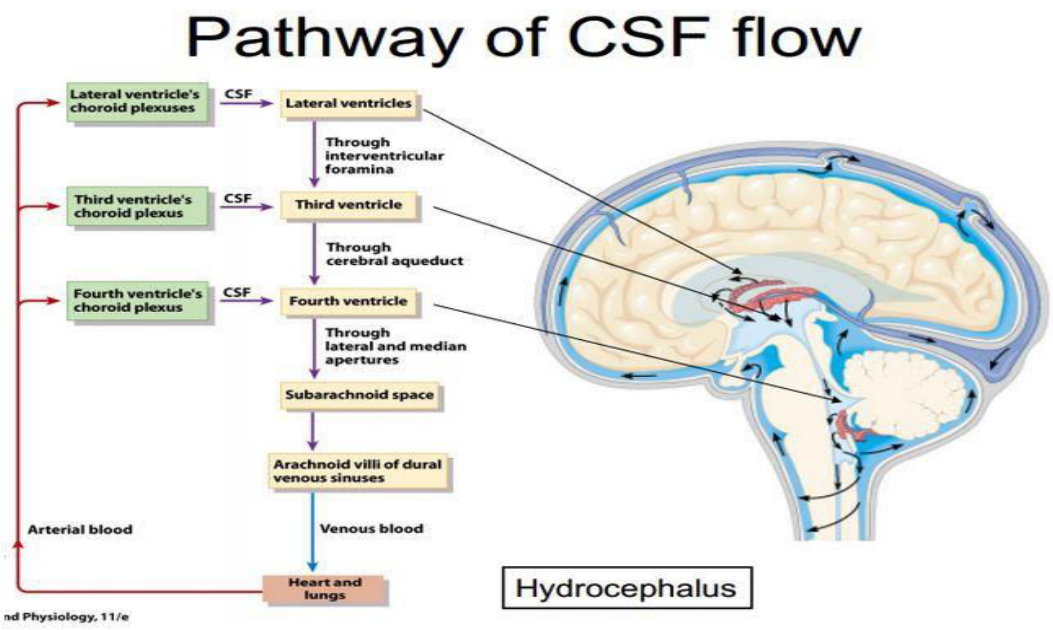
- Adrenergic nerves :diminishes CSF production
- cholinergic nerves: may double the normal CSF production rate

Production of CSF :

- In a normal child, approximately 20 mL/hr of CSF .
- The total volume of CSF approximates 50 mL in an infant and 150 mL in an adult.

❖ Most of the CSF is extra-ventricular.

CSF FLOW:



CSF absorbtion

CSF is absorbed:

- primarily by the **arachnoid villi** through tight junctions of their endothelium by the pressure forces
- **lymphatic channels** directed to the paranasal sinuses, along nerve root sleeves
- the **choroid plexus** itself.

Types of hydrocephalous:

- obstructive or non-communicating hydrocephalus(most commonly): obstruction within the ventricular system
- Non obstructive or communicating hydrocephalus: resulting from obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi.

Obstructive or non-communicating hydrocephalus

- an abnormality of the aqueduct of Sylvius or a lesion in the fourth ventricle.
- aqueductal stenosis results from:
  1. an abnormally narrow aqueduct of Sylvius that is often associated with branching or forking.
  2. In a small percentage: inherited as a sex-linked recessive trait.

- association with aqueductal stenosis :
  A. neural tube closure defects, including spina bifida occulta
  B. Neurofibromatosis.

- Aqueductal gliosis
- neonatal meningitis or a subarachnoid hemorrhage in a premature infant
- Intrauterine viral infections
- mumps meningoencephalitis
- A vein of Galen malformation.
- Lesions or malformations of the posterior fossa :
  1. posterior fossa brain tumors
  2. Chiari malformation
  3. the Dandy-Walker syndrome

Non-obstructive or communicating hydrocephalus

- a subarachnoid hemorrhage
- Pneumococcal and tuberculous meningitis
- Leukemic infiltrates.

Clinical manifestations Depends on :

- age at onset
- the nature of the lesion causing obstruction
- duration and rate of increase of the intracranial pressure (ICP).

- Enlargement of the head ….HC
- the anterior fontanel is wide open and bulging
- the scalp veins are dilated.
- forehead is broad
- eyes might deviate downward because of impingement of the dilated suprapineal recess on the brainstem tectum, producing the setting-sun eye sign.

- Long-tract signs
  1. Brisk tendon reflexes
  2. Spasticity
  3. clonus (particularly in the lower extremities),
  4. Babinski sign

- In an older child, the cranial sutures are less accommodating so that the signs of hydrocephalus may be subtler.
- common to both age groups:
  - Irritability,
  - Lethargy
  - poor appetite
  - Vomiting

- in older patients: headache is a prominent symptoms.

- A gradual change in personality and deterioration in academic productivity suggest a slowly progressive form of hydrocephalus
- head circumference often indicate an increased velocity of growth.

Examination

- Percussion of the skull: a cracked pot sound or Macewen sign, indicating separation of the sutures.
- A foreshortened occiput suggests Chiari malformation,
- a prominent occiput suggests the Dandy-Walker malformation.
- Papilledema
- abducens nerve palsies
- Pyramidal tract signs, which are most evident in the lower extremities.

Diagnosis and differential diagnosis

- Familial cases suggest X-linked or autosomal hydrocephalus secondary to aqueductal stenosis.
- A past history of prematurity with intracranial hemorrhage, meningitis, or mumps encephalitis.
- café-au-lait spots/megalencephaly…NF
- inspection, palpation, and auscultation of the skull and spine.
- head circumference
- size and configuration of the anterior fontanel
- Inspection of the back (tufts of hair, lipoma, or angioma)…spinal dysraphism

- a prominent forehead or abnormalities in the shape of the occiput
- A cranial bruit…vein of Galen arteriovenous malformation
- Transillumination of the skull.. massive dilation of the ventricular system or in the Dandy-Walker syndrome

Inspection of the eyegrounds:

1. chorioretinitis suggests an intrauterine infection, such as toxoplasmosis.
2. Papilledema(older children).

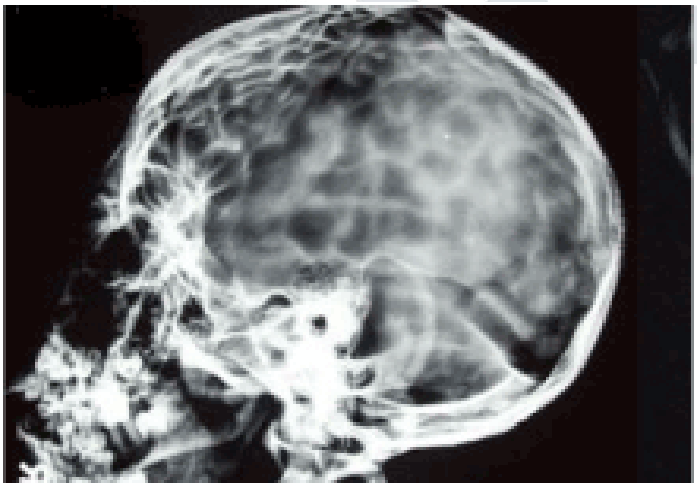
❖ The head might appear enlarged secondary to:
1. a thickened cranium resulting from chronic anemia
2. Rickets
3. osteogenesis imperfecta
4. epiphyseal dysplasia.

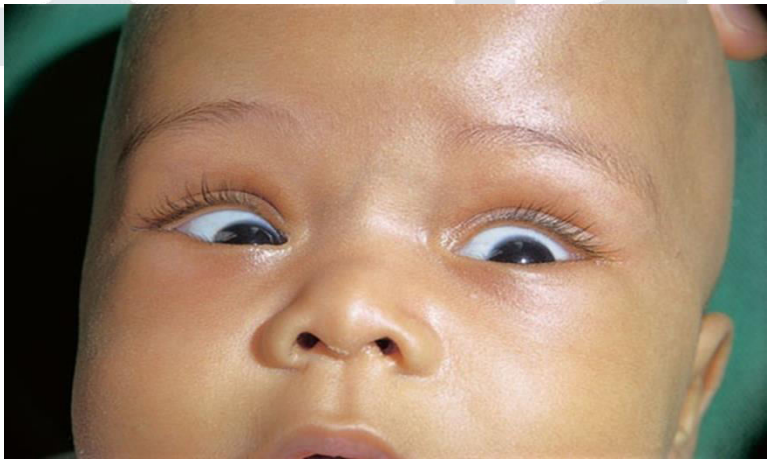
- bilateral parietal bone prominence…Chronic subdural collections
- Measurement of parents' head circumferences…Familial megalocephaly is inherited as an autosomal dominant trait and is characterized by delayed motor milestones and hypotonia but normal or near-normal intelligence.

Plain skull films:

1. separation of the sutures
2. erosion of the posterior clinoids in an older child
3. an increase in convolutional markings (beaten-silver appearance) on the inside of the skull with long-standing increased ICP

❖ The CT scan and/or MRI along with ultrasonography for cause and severity.





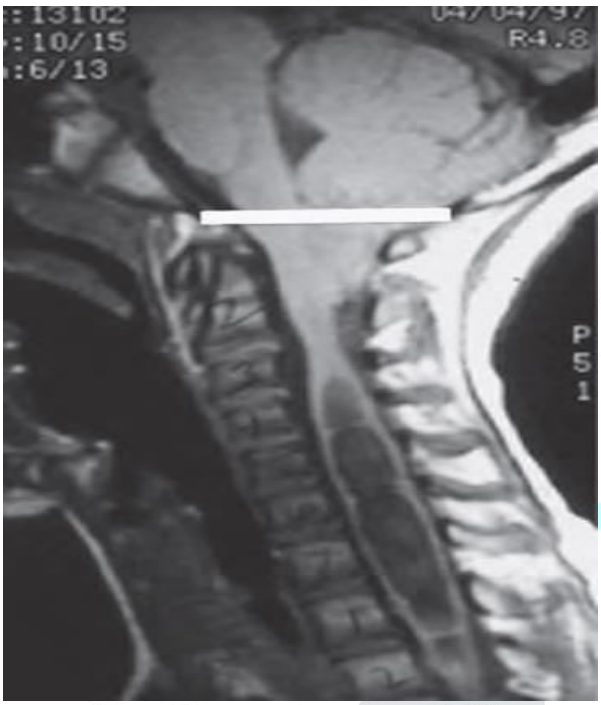
Chiari malformation

- **Type I** :displacement of the cerebellar tonsils into the cervical canal
- produces symptoms during **adolescence or adult life**
- usually **not** associated with hydrocephalus.

Patients complain :

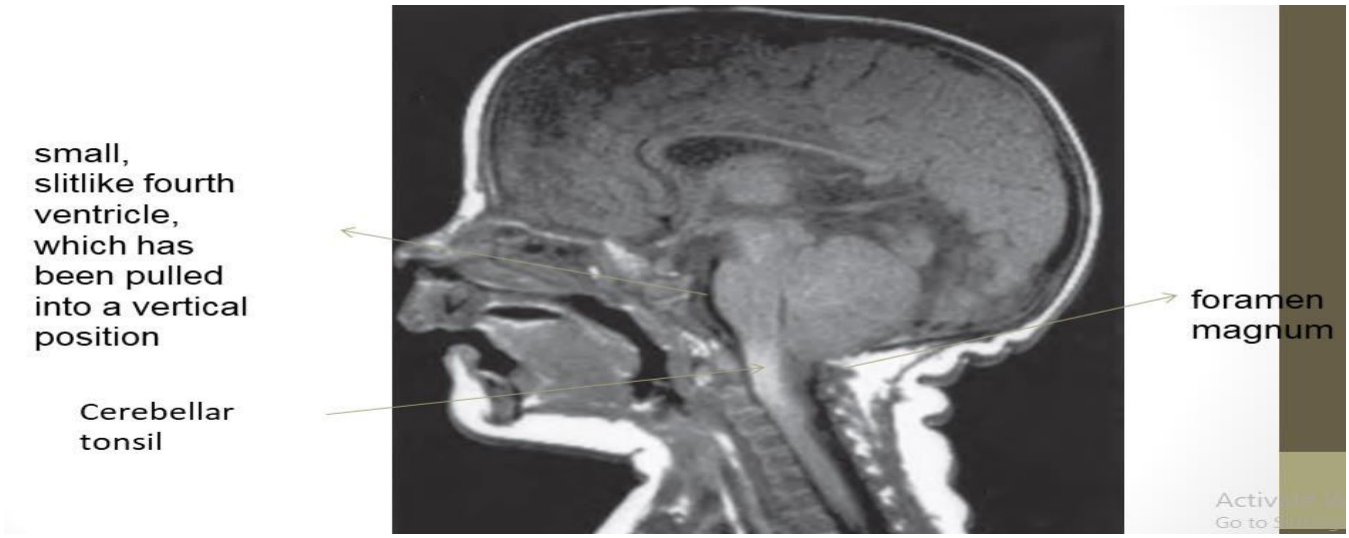
- recurrent headache
- neck pain
- urinary frequency
- progressive lower-extremity spasticity.
- **Syringomyelia** : Syrinx of the spinal cord especially the cervical region should be looked for on MRI imaging.

type I Chiari malformation:



Type II Chiari malformation

- a failure of pontine flexure development during embryogenesis, and results in elongation of the fourth ventricle and kinking of the brainstem, with displacement of the inferior vermis, pons, and medulla into the cervical canal
- Progressive hydrocephalus with a myelomeningocele.
- during infancy(10%) produce
  - Stridor
  - weak cry
  - apnea,
  - which may be relieved by shunting or by decompression of the posterior fossa.
- during childhood:
  - abnormalities of gait
  - Spasticity
  - increasing incoordination (including the arms and hands)

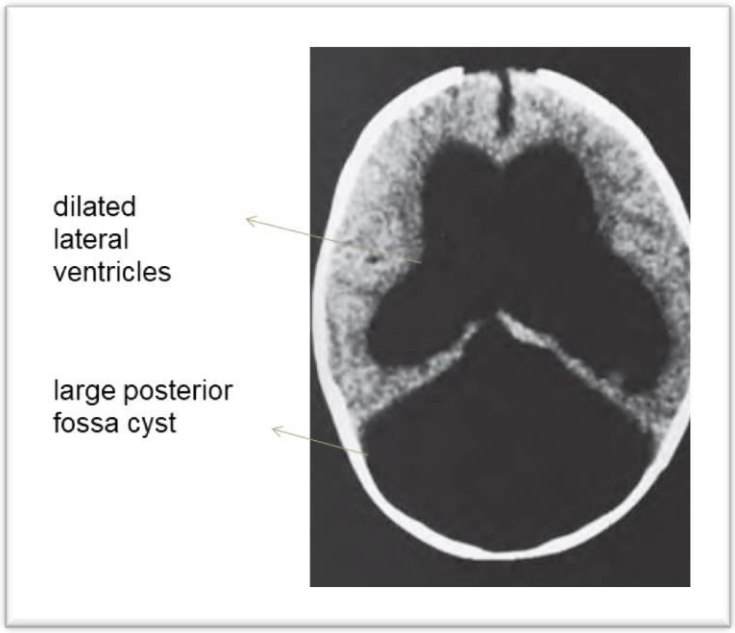


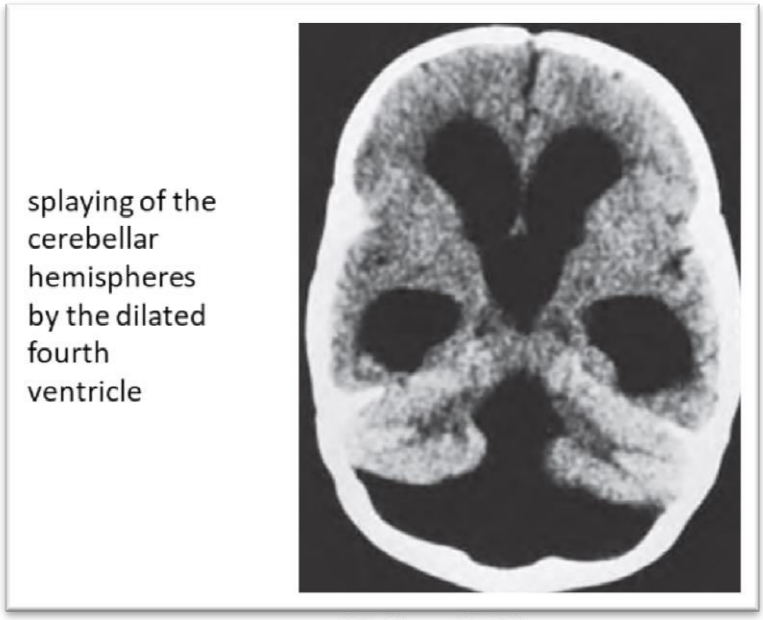
Treatment:

- surgical decompression
  If asymptomatic or mildly symptomatic patients may be managed conservatively

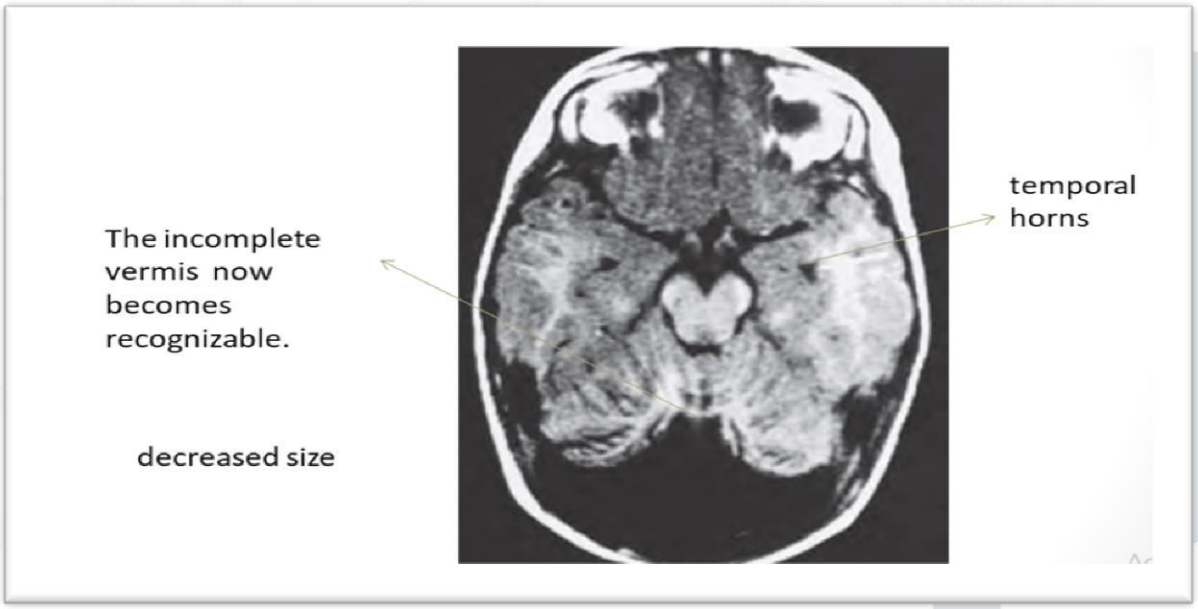
Dandy-Walker malformation

- a cystic expansion of the fourth ventricle in the posterior fossa
- midline cerebellar hypoplasia, which results from a developmental failure of the roof of the fourth ventricle during embryogenesis
- 90% of patients have hydrocephalusa.
- associated anomalies, including: agenesis of the posterior cerebellar vermis and corpus callosum.
- Infants present with :
  - a rapid increase in head size
  - a prominent occiput.
    Transillumination of the skull may be positive.
- Most children have evidence of
  - long-tract signs
  - cerebellar ataxia
  - delayed motor and cognitive milestone
    Management : shunting the cystic cavity (and on occasion the ventricles as well) in the presence of





hydrocephalus



Therapy:
depends on the cause.

1) Medical management:
use of acetazolamide and furosemide(temporarily).

2) Extra-cranial shunts, particularly a ventriculoperitoneal shunt

3) Endoscopic third ventriculostomy has evolved as a viable approach and procedure might need to be repeated to be effective.
-Ventricular shunting may be avoided with this approach.

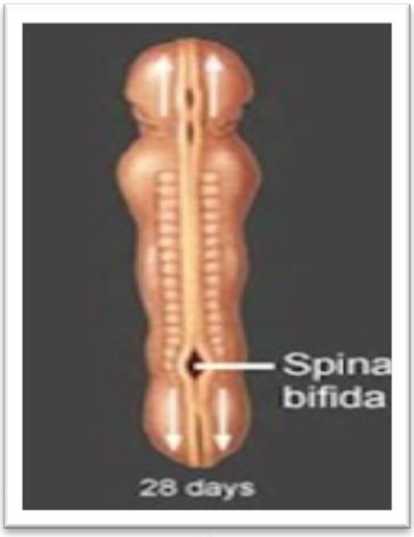
- <u>The major complications of shunting are</u> :
  - Occlusion (characterized by headache, papilledema, emesis, mental status changes)
  - bacterial infection (fever, headache, meningismus), Staphylococcus epidermidis. .
  - intrauterine surgical management of fetal hydrocephalus (high rate of associated cerebral malformations)

Prognosis

- Depends on the cause of the dilated ventricles.
- Increased risk for various developmental disabilities.
- The mean intelligence quotient is reduced particularly for performance tasks as compared with verbal abilities.
  - Abnormalities in memory function.

- Vision problems are common:
  - Strabismus
  - visuospatial abnormalities
  - visual field defects
  - optic atrophy with decreased acuity secondary to increased ICP.
  - The visual evoked potential latencies are delayed and take some time to recover after correction of the hydrocephalus.
  - some children show aggressive and delinquent behavior.
  - Accelerated pubertal development in patients with shunted hydrocephalus or myelomeningocele .

Neural tube defects



- Account for most congenital anomalies of the (CNS), (0.6-1.3 cases per 1000 live births) in the United States.

- Result from failure of the neural tube to close spontaneously between the 3rd and 4th wk of development in utero.

- Second most common disability in childhood following cerebral palsy.
- Second most common congenital anomaly after cardiac defects.

Epidemiology:

- Celtic ethnic group, as Welsh, Irish & Scotch.
- Female predominance, 60- 70% of cases.
- Geographical varitation, with England & china having higher rates.
- The incidence has declined signifacntly in the past 3 decades due to:
  1. screening techniques, as US & AFP.
  2. termination of preg.
  3. administration of folic acid.

Folic Acid

- Prevents up to 70% of NTDs.
- U.S. Public Health Service recommends that all women capable of becoming pregnant consume 400 micrograms (0.4 milligrams) folic acid daily.

Etiology: the precise cause is still unknown

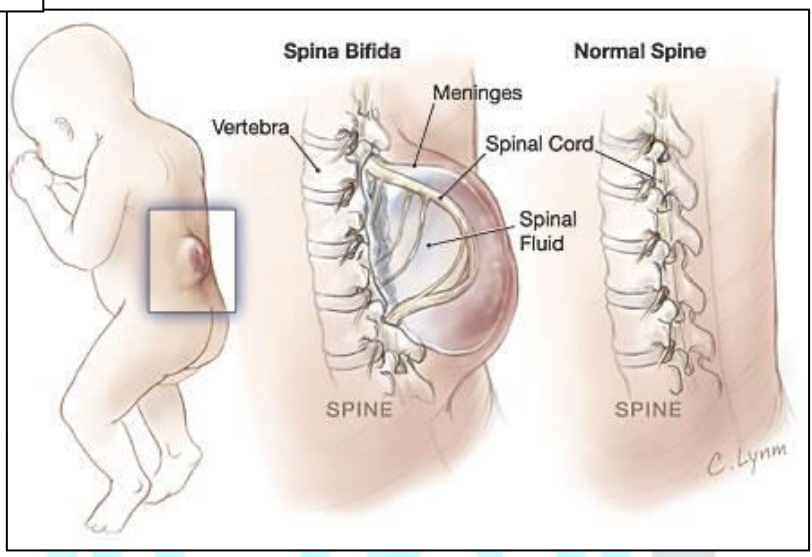
1. malnutrition.
2. medications; as antiepileptics (valproate, carbamazepine).
3. previous NTD child; increases the risk to 3%.
4. radiation.
5. certain medical conditions; as IDDM.
6. alcohol & smoking; alcohol increases the risk while smoking reduces it.

Embryology

- The primary defect is a failure of the neural folds to fuse in the midline and form the neural tube, which is neuroectoderm.
- The subsequent defect is the maldevelopment of the mesoderm, which, in turn, forms the skeletal and muscular structures that cover the underlying neural structures.
- The human embryo passes through 23 stages of development after conception, each occupying approximately 2-3 days.
- Two different processes form the CNS. The first is primary neurulation, which refers to the formation of the neural structures into a tube, thereby forming the brain and spinal cord.

- Secondary neurulation refers to the formation of the lower spinal cord, which gives rise to the lumbar and sacral elements.
- Any disruption during stages 8-10 can cause a neural tube defect (NTD).

- The neural plate is formed at stage 8 (days 17-19),
- the neural fold occurs at stage 9 (days 19-21),
- and the fusion of the neural folds occurs at stage 10 (days 22-23).



Detection:

Prenatal screening:

1. maternal AFP in the 15 - 20 wk.
2. amniotic AFP.
3. US is 95% specific.

- AFP is the major serum protein in early embryonic life and is 90% of the total serum globulin in a fetus.
- it's first made in the yolk sac and later in the GI system and liver of the fetus.
- Serum maternal AFP measurement of more than 1000ng/ ml is abnormal. & could be :
- Anencephaly , Spina bifida cystica Encephalocele (leaking), Conjoined twins, Omphalocele, Turner syndrome,Gastroschisis ,Exstrophy of the cloaca , Oligohydramnios & fetal death.

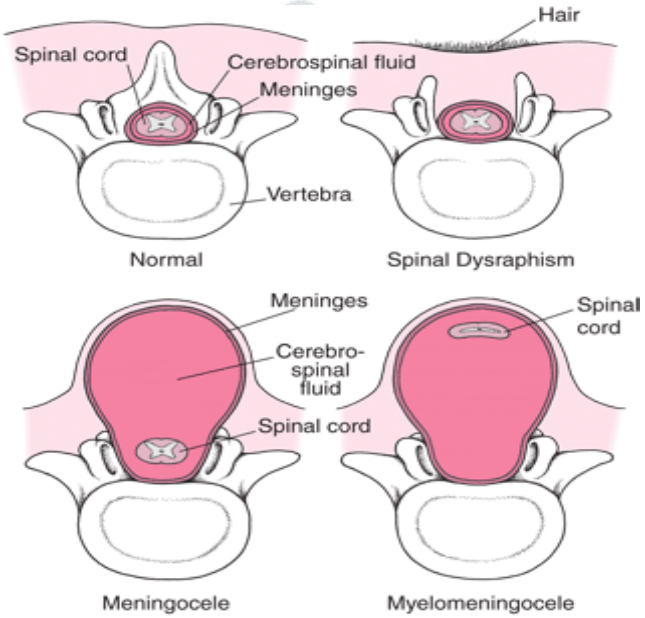
Pathology:

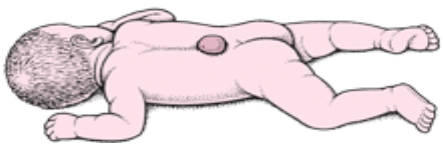
- neural tube defects can be open (neural structures that communicate with the atmosphere) or closed (skin covered). They can be ventral or dorsal midline defects.

The major neural tube defects

1) Spina bifida:
   - Occulta
   - Aperta
   - Cystica; meningocele & myelomeningocele.or

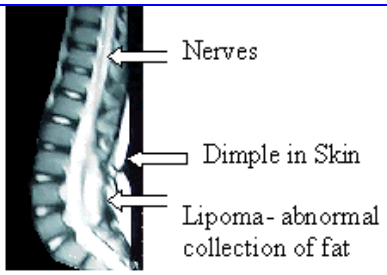
2) bifid cranium;
   - Bifid cranium occultum.
   - Encephalocele .
   - Anencephaly .





3) Bifid cranium occultum:
   - The most benign type of cranium bifidum occultum is the persistent parietal foramina or persistent wide fontanelle.
   - The parietal foramina can be transmitted as an autosomal dominant trait via a gene located on the short arm of chromosome 11.
   - mostly asymptomatic, & most of these skull defects close over time.

Spina Bifida Occulta



MRI of Underlying Abnormality (Lipoma)

- The post. Vertebral arch has a closure defect within it, but there is no herniation of the neural tube .
- It's found in up to 10% of the population.
- Most individuals are asymptomatic and lack neurological signs .
- No hydrocephalus or Chiari II malformation.
- Cutaneous stigmata as a hairy patch, dermal sinus tract, dimple, hemangioma, or lipoma may exist and point to the underlying spina bifida,

Other signs that should elucidate your suspicion:

- Radiologic signs ; Hemivertebrae ,Scoliosis
- Orthopedic findings; as asymmetry or foot deformities
- Neurological problems: as weakness, atrophy or asymmetry, loss of sensation, painless sores, hyperreflexia ,unusual back pain, radiculopathy
- Urologic problems ; as Neurogenic bladder or incontinence

- A spine X-ray shows a defect in closure of the posterior vertebral arches and laminae, typically involving L5 and S1.
- There is no abnormality of the meninges, spinal cord, or nerve roots .
- occasionally associated with more significant developmental abnormalities of the spinal cord, including syringomyelia, diastematomyelia, and a tethered cord.
- The cord is occasionally tethered by a shortened thickened filum terminale (hypertrophic).

Impairments associated with Spina Bifida

- **Physiological** changes below the level of the lesion generally include: abnormal nerve conduction, resulting in:
  - somatosensory losses
  - motor paralysis, including loss of bowel and bladder control

- **Anatomical** changes below the level of lesion:
  - musculoskeletal deformities (scoliosis)
  - joint and extremity deformities (joint contractures, club foot, hip subluxations, diminished growth of non-weight bearing limbs)
  - osteoporosis.

meningocele & myelomeningocele

Meningocele

A meningocele is formed when the meninges herniates through a defect in posterior vertebral arches, or anterior sacrum.

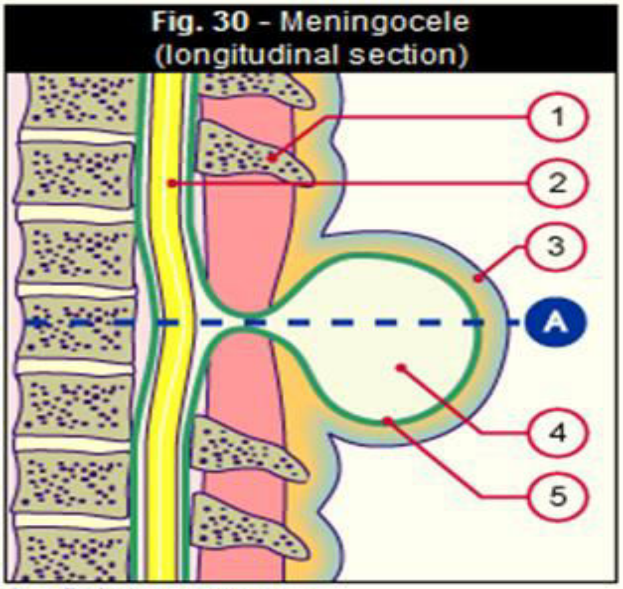


Fig. 30 - Meningocele (longitudinal section)

1 Spinous process
2 Spinal cord
3 Mostly intact skin over the meningocele
4 Meningocele with cerebrospinal fluid
5 Dura mater

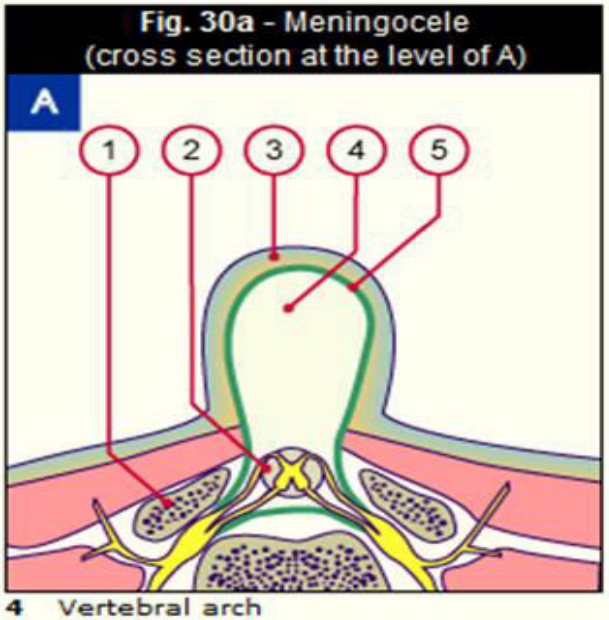
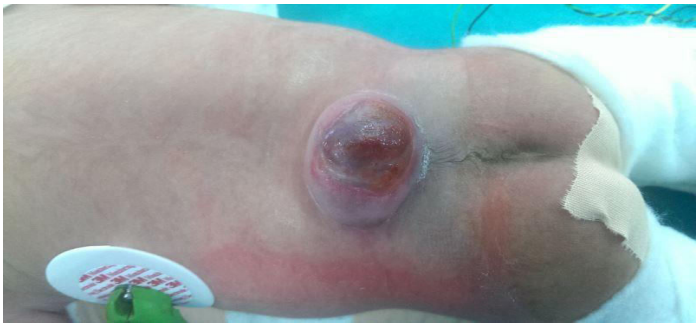
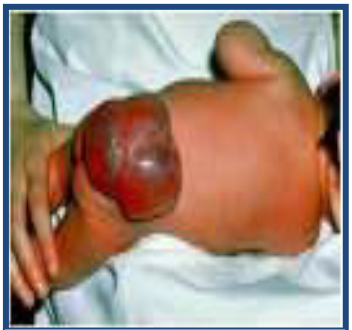


Fig. 30a - Meningocele (cross section at the level of A)

4 Vertebral arch
2 Spinal cord
3 Mostly intact skin over the meningocele
4 Meningocele with cerebrospinal fluid
5 Dura mater

- The spinal cord is usually normal and assumes a normal position in the spinal canal, although there may be tethering of the cord, syringomyelia, or diastematomyelia.
- A fluctuant midline mass that may transilluminate occurs along the vertebral column, usually in the lower back. Most meningoceles are well covered with skin and pose no immediate threat to the patient.
- In asymptomatic children with normal neurolgic findings and full thickness skin covering the meningocele, surgery may be delayed or sometimes not performed.





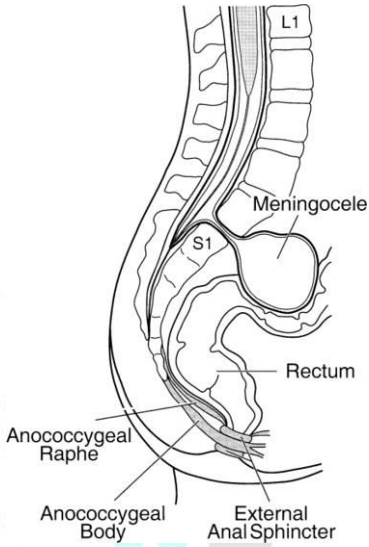
- The least common form of spina bifida.
- In a **posterior meningocele**, the outer faces of some vertebrae are open (unfused) and the meninges are damaged and pushed out through the opening, appearing as a sac or cyst which contains cerebrospinal fluid.

- In an **anterior meningocele**, the inner faces of vertebrae are affected and the cyst protrudes into the retroperitoneum or the presacral space.

An anterior meningocele comes with Symptoms of:

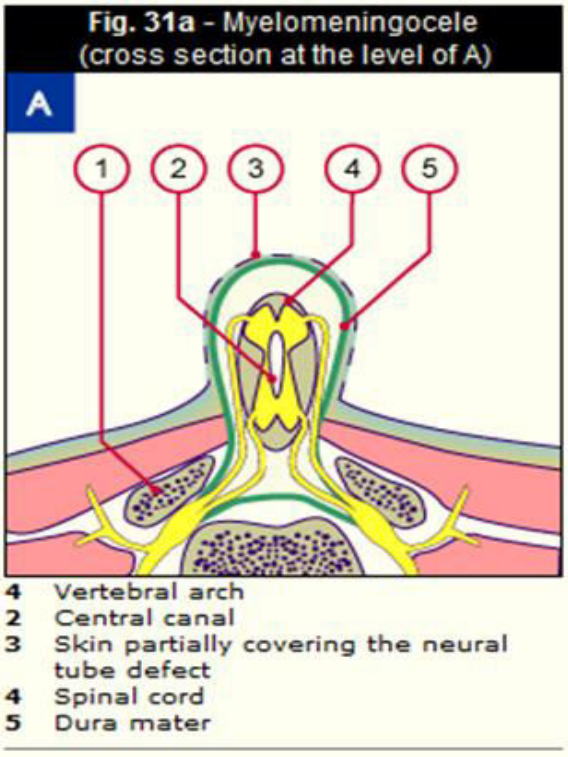
1) constipation .
2) bladder dysfunction .
3) Female patients may have associated anomalies of the genital tract, including a rectovaginal fistula and vaginal septa .

- Plain X-ray demonstrate a defect in the sacrum.
- And CT scanning or MRI outlines the extent of the meningocele .

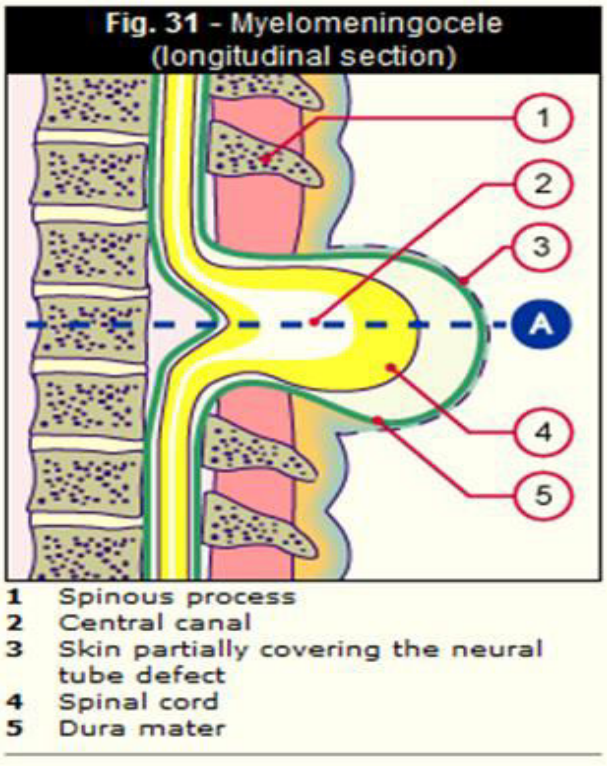


Myelomeningocele

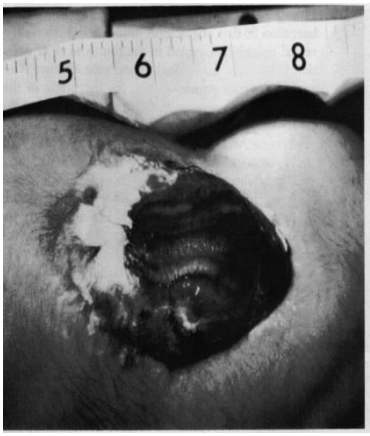
- Characterized by protrusion of the neural elements through a vertebral defect into a meningeal lined sac .
- Typically, the cord at this level is not fused. but is in it's flattened embryological state , with the nerve roots arising from the ventral surface & the open central canal lying dorsally.
- Remnants of neural tissue are visible beneath the membrane, which may occasionally rupture and leak CSF.



4 Vertebral arch
2 Central canal
3 Skin partially covering the neural tube defect
4 Spinal cord
5 Dura mater



1 Spinous process
2 Central canal
3 Skin partially covering the neural tube defect
4 Spinal cord
5 Dura mater



- Myelomeningocele represents the most severe form of dysraphism involving the vertebral column and occurs with an incidence of approximately 1/2,000 live births.
- A myelomeningocele may be located anywhere along the neuraxis, but the lumbosacral region accounts for at least 75% of the cases.

Etiology

- The cause of myelomeningocele is unknown.
- a genetic predisposition exists; the risk of recurrence after one affected child increases to 3–4% and increases to approximately 10% with two previous abnormal pregnancies.
- There is strong evidence that maternal periconceptional use of folic acid supplementation reduces the incidence of neural tube defects in pregnancies at risk by at least 50% .
- To be effective, folic acid supplementation should be initiated before conception and continued until at least the 12th wk of gestation when neurulation is complete.
- In normal risk pregnancies, women should take 0.4 mg of folic acid daily. And in high pregnancy (previously affected child), supplementation should be started 4 mg daily, beginning 1 month prior to planned conception.
- Certain drugs—including drugs that antagonize folic acid such as trimethoprim and the anticonvulsants: Valproic acid, carbamazepine, phenytoin, and phenobarbital increase the risk of myelomeningocele.
- Valproic acid causes NTDs in approximately 1-2% of pregnancies whe administered during pregnancy.

Clinical Manifestations

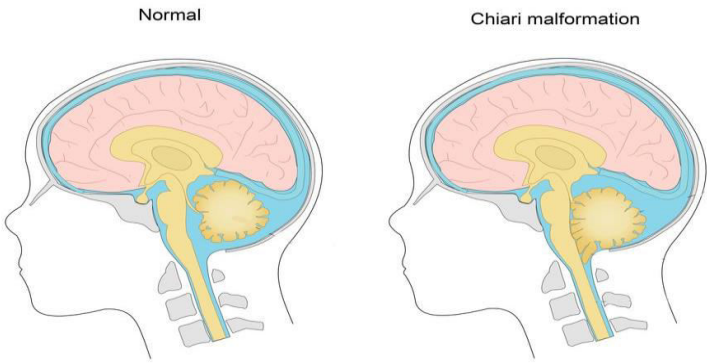
- The condition produces dysfunction of many organs and structures, including the skeleton, skin, and genitourinary tract, in addition to the peripheral nervous system and the CNS.
- *lesion in the low sacral region* causes bowel and bladder incontinence associated with anesthesia in the perineal area but with no impairment of motor function.
- Newborns with a defect in the midlumbar region typically have a saclike cystic structure covered by a thin layer of partially epithelialized tissue

- **Examination of the infant shows**
  - a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes,
  - a lack of response to touch and pain
  - and a high incidence of postural abnormalities of the lower extremities (including clubfeet and subluxation of the hips).
  - Constant urinary dribbling and a relaxed anal sphincter may be evident.

❖ Hydrocephalus in association with a type II Chiari defect develops in at least 80% of patients with myelomeningocele.

❖ Generally, the lower the deformity in the neuraxis (e.g., sacrum), the less likely is the risk of hydrocephalus.

*Congenital downward displacement of cerebellar vermis and tonsils through the foramen magnum:



- Ventricular enlargement may be indolent and slow growing or may be rapid, causing a bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting associated with an increased head circumference.

- Not infrequently, infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain dysfunction, including difficulty feeding, choking, stridor, apnea, vocal cord paralysis,pooling of secretions, and spasticity of the upper extremities, which, if untreated, can lead to death.

Management (Multidisciplinary team approach**)**

1. Assessment of the sac & it's coverings.
2. Neurological examination
3. Examination for other associated conditions.
4. **Counseling & careful discussions with the parents.**
5. Surgical procedures.

Treatment:

- Surgery can be delayed for several days (except when there is a CSF leak)
- most infants require a shunting procedure for hydrocephalus.

Prognosis :

- For a child who is born with a myelomeningocele and who is treated aggressively, the mortality rate is approximately 10–15%, and most deaths occur before age 4 yr.

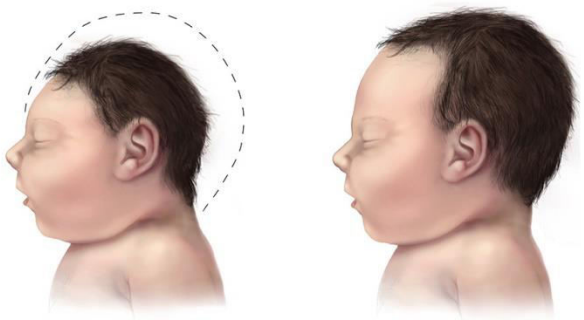
- At least 70% of survivors have normal intelligence, but learning problems and seizure disorders are more common than in the general population.

- Because myelomeningocele is a chronic handicapping condition, periodic multidisciplinary follow-up is required for life.

Microcephaly , Encephalocele & Anencephaly

Microcephaly

- Microcephaly is defined as a head circumference that measures more than 3 SD below the mean for age and sex
- This condition is relatively common, particularly among developmentally delayed children
- Subdivided into 2 main groups:
  1. Primary (genetic)
  2. Secondary (non-genetic)



Primary Microcephaly

- Refers to a group of condition that usually have no associated malformations **or** are associated with a specific genetic syndrome
- Affected children are usually identified at birth

Causes:

- Familial (Autosomal Recessive)
- Autosomal Dominant
- Syndromes: Down, Edward, Cri-du-Chat, Cornelia de Lange, Rubinstein-Taybi, and Smith-Lemli-Opitz
- X-Linked

Secondary Microcephaly

- Results from a large number of agents that can affect a fetus in utero or an infant during periods of rapid brain growth, particularly the first 2 years of life
- May be identified at birth or later

Causes:

- Congenital Infections: CMV, Rubella, Toxoplasmosis
- Drugs: Alcohol, Hydantoin
- Radiation
- Meningitis/Encephalitis
- Malnutrition
- Hyperthermia
- HIE
- Syndromes: Rett, Seckel, Angelman

Clinical Manifestations:

- Small Head Circumference, Sloping Forehead, and Small Anterior Fontanelle
- Developmental Impairments
- Organ Malformation

- Visual Impairment
- Hearing Loss
- Learning Difficulties
- Seizures
- Movement Disorders

Diagnosis:

- Investigations are determined by the history and physical examination. If the cause is unknown:
- Mother's serum phenylalanine level (brain damage)
- Karyotype (chromosomal syndromes)
- MRI (structural abnormalities of the brain)
- CT (intracerebral calcifications)
- Fasting plasma and urine amino acid analysis
- Serum ammonia
- TORCH titers, HIV testing, and urine culture (CMV)

Treatment:

- No specific treatment to fix microcephaly
- Supportive genetic and family counseling
- Placement in an appropriate program that will provide for maximal development of the child
- Controlling seizures and neuromuscular symptoms
  Adequate nutrition

Encephalocele

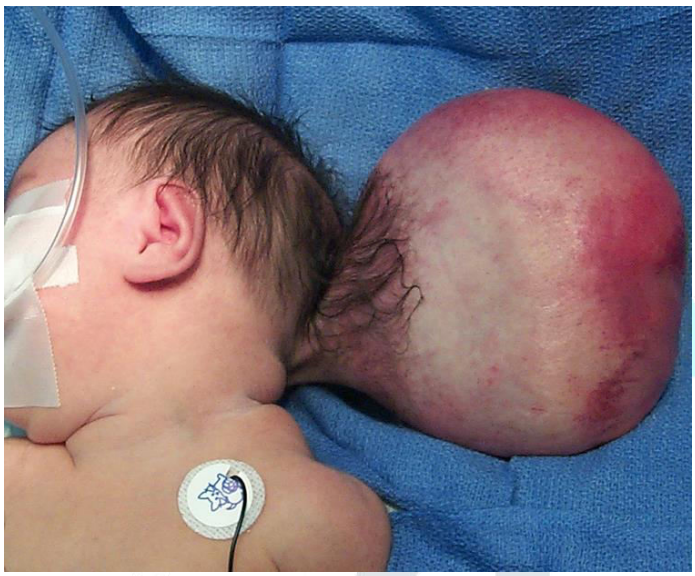
- An encephalocele is a protrusion of the brain through a defect in the skull (cranium bifidum) that is "closed" or covered with skin
- Cranial encephalocele contains the sac plus cerebral cortex, cerebellum, or portions of the brainstem
- It could be Primary (congenital) that present at birth, its major types are: sincipital, basal, occipital. It could be Secondary (acquired) due to trauma or post-surgical defects
- The cranial defect occurs most commonly in the occipital region at or below the inion.
- Frontal or nasofrontal encephaloceles are also common in certain parts of the world. Some frontal lesions are associated with cleft lip/palate
- Patients are at increased risk for developing hydrocephalus, because of: aqueductal stenosis, Chiari malformation, or the Dandy-Walker syndrome

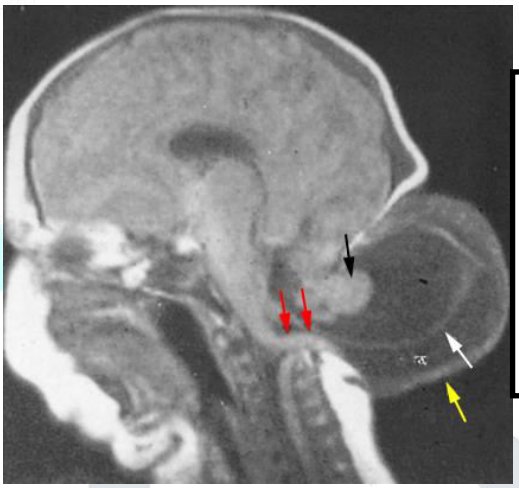
Meckel-Gruber Syndrome

- Cranial encephalocele is most commonly part of a syndrome called Meckel-Gruber syndrome.
- It is a rare autosomal recessive condition that is characterized by:
  - Occipital encephalocele
  - Cleft lip/palate
  - Microcephaly
  - Microphthalmia
  - Abnormal genitalia
  - Polycystic kidneys
  - Polydactyly

Clinical Manifestations

- The clinical features of encephalocele are variable depending upon the type (location) and severity
- Sincipital encephaloceles may be occult lesions that are not noticeable or may present with *marked craniofacial deformities*
- Basal encephaloceles may or may not be apparent on external inspection. Affected patients may present as: *a nasal or epipharyngeal mass, difficulty breathing, recurrent upper tract infections, nasal discharges, recurrent meningitis, or CSF leaks*
- Occipital encephaloceles usually are obvious at the time of birth
  - Those of relatively large size may be associated with *cranial nerve deficits, poor sucking and feeding, spasticity, blindness, seizures, or developmental delay*
  - Neurologic deficits may progress after birth if hydrocephalus develops
  - Occipital encephalocele also may be associated with hind-brain anomaly (Chiari III malformation)





MRI demonstrating a Chiari III malformation with cervico-occipital encephalocele

Diagnosis:

- The diagnosis is apparent at birth in most of the occipital encephaloceles
- Basal encephaloceles may present as a midline mass in the nose or may not be visible. They also tend to present with meningitis
- An encephalocele may be mistaken for a nasal polyp if it is located within the nose or for a soft tissue tumor if it is covered with skin and anterior to the nose.
- Transillumination of the sac can indicate the presence of neural tissue.
- X-ray of the skull and cervical spine
- Ultrasonography is most helpful to identify the contents of the sac
- MRI and CT
- Diagnosis in utero is possible by: maternal serum AFP levels, U/S, MRI

Treatment:

- If diagnosed prenatally, vaginal delivery is safe if the lesion is small. C/S is required if the lesion is large
- Surgical treatment is appropriate in most cases (removing the overlying sac and closing the defect)

Prognosis:

- Patients are at risk for vision problems, microcephaly, intellectual disability, and seizures
- Patients with neural tissue within the sac and associated hydrocephalus have the poorest prognosis

Anencephaly

- It is an open defect in the calvaria, meninges, and skin, such that the cranial neural tube is exposed
- It results from failure of the rostral neuropore to close around postovulatory day 25
- It is a severe defect and is not compatible with survival. Infants that are alive at birth generally die within hours, but occasionally survive for a few days or weeks
- Incidence is 1 in 1,000 (most end in miscarriage). Recurrence is common

Clinical Features:

- In the most common type of anencephaly, the forebrain and variable amounts of upper brainstem are involved
- Exposure in utero results in destruction of neural tissue, which appears as a hemorrhagic, fibrotic, nonfunctioning mass
- The hypothalamus is typically missing. The cerebellum, brainstem, optic nerves, and spinal cord may be malformed. Underdevelopment or absence of the pituitary leading to adrenal hypoplasia is always present
- The frontal, parietal, and portions of the occipital bones are most often affected
- The absent cranial vault results in the characteristic appearance of bulging eyes and absent neck
- The defect in the skull sometimes extends through the level of the foramen magnum and involves the cervical spine (holoacrania)
- Neonates typically have brainstem function, with spontaneous breathing and often with suck, root, and gag responses. However, they are permanently unconscious

Additional Anomalies

- Folding of the ears
- Cleft lip/palate
- Congenital heart defects
- Omphalocele
- Pulmonary, renal, and skeletal malformations
- Aganglionosis

Diagnosis:

- Maternal serum AFP level
- Fetal ultrasonography

Management & Prevention:

- Prenatal detection is usually followed by termination of the pregnancy
- There are no neurosurgical management options
- Prevention is the most important aspect of management of anencephaly
- Periconceptional folic acid supplementation is recommended, higher doses are recommended for women taking anticonvulsants or has previous history of anencephaly

Thalassemia

- Commonest genetic disorder
- Inherited by reduced or absent production of one of globin chains.
- Disruption of the balance between the production of α and non-α globin chains.

- α - thalassemia → deletion
- β- thalassemia → deletion, region mutation, termination or other mutaions.

β thalassemia :

. ↑ α globin chains which interact with RBCs membrane and ↓ its survival→ anemia + erythroid production
. Gamma production in normal amount →↑ HbF
. -d- globin is also in normal amount →↑ HbA2

Types :

1. Minor→ heterozyocity (asymptomatic)
2. Intermediate → can survive without transfusion
3. Major (cooly's anemia) → needs intensive transfusion.

. All forms has hypochromic, microcytic anemia.

Thalassemia major :

- No produduction or small amount
- Severe hemolysis + ineffective erythropoiesis → severe anemia
- Appears at age of 3-6 months when γ start to shift to β
- Presentation:
  - ► Initially related to anemia → pallor or jaundice (hemolysis) , ↓ activity and sleeping, then due to compensatory ineffective erythropoiesis .
  - ► Thalassemic face (maxillary hyperplasia, flat nasal bridge, frontal bossing) + pathological bone fractures + marked hepatospleenomegaly.
  - ► Features of ineffective erythropoiesis :
    1- Hepatospleenomegaly
    2- Extramedullary hematopoiesis and ↑ metabolic need.
    3- Expansion of medullary space with massive expansion of marrow of the face and skull → thalassemic face.

How to approach ?

1. **Hx**
   أهم نقطة أسأل لو الأهل عملوا فحص أو لو في حدا من قرايبه, لو الأم ما بتعرف اسأل عن لو حدا من قرايبه استأصل طحال أو بروح ينقل دم دوري

2. **Examination**
3. **Investigations :**

- CBC + blood film

1. Mycrocytic hypochromic anemia anemia
2. Target RBCs
3. Reticulocytopenia
4. Nucleated RBCs (immature)
5. Anisopoikilocytosis

Hb < 6g\dL progressively unless transfusion happen

Retic < 8% inappropriate low when anemia measured.

- chemistry + bilirubin : only unconjugated bilirubin is high initially then they start to increase even if the child didn't receive blood → iron will accumulate
↑serum ferritin + transferrin

- radiology to detect any bone marrow hyperplasia

How to Dx ?

best or 1st line is high performance liquid cchromatography, then electrophoresis (only in β type, in α you need genetic study), then absent or very low HbA, 98% HbF, 2% HbA2.

Management and treatment:

1- Long term transfusion therapy
2- Iron chelating agent
3- Spleenectomy
4- Allogenic hematopoietic transplant
5- Supportive measures.

Transfusion:

- Should confirm the need of transfusion by laboratory + clinical methods.
- Transient need due to parvovirus doesn't mean that the pt is dependent on transfusion.
- Long term observation: for chronic transfusion.
- Determine the need according to growth, bone changes, hemoglobin.

Transfusion complications :

☒ Hemosiderosis

- 1 µ of packed RBCs → 1 mg iron
- Liver develops after 1 yr of chronic transfusion
- It affects endocrine system:

1- Hypogonadotrophic gonadism
2- Hypothyroidism
3- Hypoparathyrodism
4- Growth hormone diffeciency 5-DM

☒ After 10 yrs of chronic transfusion:
cardiac complications (failure and\or arrhythmia) → who don't receive chelating agent.

How to monitor iron overload?

1- Serum ferritin level (serial)
2- Non-invasive measurement of organ injury is improving iron tt.
liver and cardiac (standard) and soon pancreatic + gonadal.
T2 MRI after 7 yrs of transfusion

- Rate of tissue loading and efficacy of chelating agents creates a discrepancy between liver and heart iron.

- Goal of transfusion ≈ Hb 10g\dL

When to give chelating agent ?
goal is prevention of iron tissue injury. After 10 transfusions or when serum ferritin>1000 mg\ml, liver iron > 2500 µ g\g

3 types of chelating :

1- Deferoxamine
2- Deferasirox
3- Deferiprone

Defroxamine "desferal" :

- Excellent safety and efficacy
- SC or IM , for 8 hr (at least) ,5-7 days\week (because of short half-life , less than 30 min)
- That's why the patients re non-comliant to it (major problem).
- Start at 20mg\kg then increase up to 60 mg\kg in heavily loaded pts.
- Adverse effects : 1- retinal changes 2- ototoxicity 3- bone dysplasia with truncal shortening

Deferasivox (exjade) :

- Oral, once daily with dispersible in water
- Half-life > 16 hrs, start with 20 mg\kg and gradually up to 30 mg\kg
- Most serious side-effect → kidney damage
- Most common side effect → GI symptoms

Hydroxyuvea

- DNA antimetabolite →↑ stress erythropoiesis →↑ HbF
- Used in suckle cell and some β -intermedia cases.
- Limited effect in β -thalassemia.

<u>Spleenectomy</u> :

- only in patients who develop hyperspleenism.
- These patients has ↓ steady state of Hb and\or ↑ transfusion requirement, but there is a serious side effect of for spleenectomy:
- Infection → immunization against encapsulated bacteria + long term penicillin prophylaxis + instructions regarding fever managmeny.

- In intermedia venous thrombosis, pulmonary HTN, leg ulcers, silent cerebral infarction .
  (higher risk than pts with spleenectomy)

β- thalassemia intermedia (non-transfusion dependent)

- They are initially not chronic transfusion pts in infancy but sporadically need transfusion throughout their life time .
- They have the gene modifiers hat worsen the condition .
- They have significant ineffective erythropoiesis
  Hb ≈ 7g\dl (range 6-10 g\dL)
- These pts have some complications of thalassemia major (non-transfusion) but severely varies depending on degree of erythropoiesis.
  1- Medullary hyperplasia
  2- Hepatospleenomegaly
  3- Pulmonary HTN
  4- Growth failure
  5- Thrombotic events
  6- Hematopoietic psudotumor.

- Due to ↑ GI absorption of iron → they may develop hemosiderosis so use chelating agents.
- Transfusion is indicated in pts with significant morbidities.
- Extramedullary hematopoiesis → can happen in vertebral canal → causes compression on spinal cord → neurological symptoms → medical emergency later on .
- Sometimes in peds, it's missed with iron deficiency due to same results on CBC, so we may start a course of iron (it's more prevalent) then re-evaluate the condition. (Iron will improve, thalassemia won't)
- with treatment :
  Pts with thalassemia →↓ MCU but normal RDW
  iron diff →↑ RDW
- thalassemia on Hb analysis →↑ HbF and elevated HbA2.
- If family Hx is suggestive → further investigations needed.
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Thalassemia in newborn

- ↑ (γ 4) bart's hemoglobin in fetal life and presented at birth
- Differnent phenotypes results from one or both –globin deletion.
- If 1α-globin (silent) → not identified hematologically
- No change in MCU
- Usually Dx → when they have baby with 2 gene deletions.
- But some pts → in screening program may have ↓ Bart Hb.
  (in newborn period Hb Bart <3%) normally but have >25%
- If 2α-globin → thalassemia trait (trans or cis mutation)
- If combined with other mutations → α -thalassemia major.
- Africa → trans deletion

- Asia or Mediterranean regions → cis

HbH → deletion of 3 –globin

- Most severe form → non deletional α –globin mutation + 2 allele deletion
- HbH constant spring (α -\ α , α cs)
- Commonest non-deletional type.
- Dx : by Hb bart > 25 + evidence from parents
- We need genetic study (DNA analysis) → definitive Dx.
- We may rarely use brilliant crystal blue → can stain HbH.
- HbH → has marked anemia, mycrocytic, mild splenomegaly.
  occasionally → scleral icterus or cholithiasis.
- No indication for chronic transfusion (Hb 7-11 g\dL, MCV 51-73), but if anemia worsen we may need intermittent transfusion.
- Treatment :
  1- Monitor growth and organ dysfunction
  2- Folate + multivitamin supplement without iron.

- Older patients may have ↓ calcium and V.D.
- In HbH → infection may happen
- Spleenectomy → occasionally indicated , due to post spleenectomy thrombosis, we can give aspirin or other anticoagulants after surgery.
- Hemosiderosis due to ↑ exposure to transfusion or due to ↑ GI absorption, develops in pts and need therapy.
- HbH → unstable and sensitive to oxidative agent → avoid them

Deletion of 4 α –globin → profound anemia → hydrops fetalis

- no normal Hb at birth (Bart, Portland, Gower 1 and 2)
- In fetal survive → immediate exchange transfusion.
- These are severe α –thalassemia (transfusion dependent)
- Only cure is hepatopoietic stem cell transplantation.
- If parents are high risk to have hydrops fetalis → offer molecular study → Dx in early pregnancy
- Later on, intrauterine transfusion can improve fetal survival but :
  1- Chronic transfusion 2- bone marrow transplant

Congenital immunodeficiencies

- **The commonest:** B-cell
- Impaired ability to produce normal immune response, and mostly genetic.
- Presented as recurrent infections, and affect adaptive or innate immunity.

- Innate is the first line defense then the adaptive.
  innate includes:
  1- soluble factors → chemokines, cytokines, acute phase proteins
  2- cellular components → neutrophils, monocytes, macrophages, natural killers

- Adaptive → T and B lymphocytes and their effector molecules.

- Frequency of certain infections in childhood:
  1- URTI maximum up to 8 times
  2- Otitis media up to 6
  3- Diarrhea up to 2

- Most of recurrent infections (90%) due to 2ndry cause not immune deficiency.
- **2ndry causes** of recurrent infections:
- **Viral**: HIV, measles, rubella, influenza
- **Metabolic**: DM, malnutrition, uremia, sickle cell disease, burns, zinc & vitamin deficiencies, multiple **carboxylase deficiency**.
- **Protein losing state**: nephrotic syndrome, protein losing enteropathy.
- **Other causes**:
  - prematurity, acquired asplenia, sarcoidosis, SLE and autoimmune d.
  - acquired neutropenia (autoimmune, viral infection, drug induced)
  - immunosuppressive agents(steroids, radiation, antimetabolites)
  - stem cell transplant\graft-hvs host
  - malignancy (leukemia, non-lymphoid, Hodgkin.

When to suspect immunodeficiency?
- frequency, severity, location of infection and pathogen + age of symptoms onset.

- **By Hx:**
  1- Recurrent sinopulmonary with encapsulated bacteria → B-cell
  2- FTT, diarrhea, malabsorption + opportunistic infection (fungi, candida, pneumocystic, carinii) → T-cell
  3- Viral infections → T-cell or natural killers
  4- Delay cord separation especially with omphalitis and →later on periodontal disease + poorely formed abscess → leukocyte adhesive
  5- Deep seated abscesses + recurrent skin infections with staph aureus, asperigillus, serratia marcescens → neutrophils function
  6- Severe and recurrent skin and respiratory infection → complement

- **Associated problems:**
  1- Atoxic telangiectasia
  2- Di George syndrome (chronic heart disease, hypocalcaemia)
  3- Atopic dermatitis (hyper IgE syndrome, omen syndrome)
  4- Easy bruising or bleeding disorders (Wiskott-aldrich syndrome)

- Family Hx of primary immunodeficiency or death in young children due to infections.

- **10 warning signs of primary immunodeficiency:**
  1- One or more ear infections in 1 yr
  2- 2 or more serious sinus infection
  3- 2 or more pneumonia in 1 yr
  4- 2 or more months on antibiotics with little effect
  5- Recurrent deep skin\organ abscesses
  6- Failure of infant to gain wt or row normally.
  7- 2 or more deep seated abscess.
  8- Need for IV antibiotics to clear infections
  9- Family Hx of immunodeficiency
  10- Persistent thrush in mouth or elsewhere in skin after age of 1 yr

By examination: recurrent infection in immunodeficiencies associated with pathology at infection site → morbidity like scaring of tympanic membrane → heaving loss

1- Height, wt, nutritional status and subcutaneous fat.
2- Oral thrush, purulent nasal or ear discharge, chronic rales
3- Absence of tissue (tonsils) → agammaglobinemia
4- Increased size of lymphoid tissue → CVID or HIV (common variable)
5- Eczema, petieches or bruises → wiskott-aldrich syndrome

B-cell immunodeficiencies:

1- IgA deficiency
2- IgG subclasses deficiency
3- Common variable immunodeficiency
4- X-linked agammaglobulinemia
5- Transient hypogammaglobulenemia of infancy

- Pluripotent stem cell (in bone marrow) → lymphoid precursor cell → PRO-B cell → PRE-B cell → immature B-cell → (then to spleen) → mature B-cell (native) → (blood and lymph) → plasma cells

X-linked agammaglobulinemia:

- Mutation in the gene encoding bruton tyrosine kinase (BtK) on Xq22 (and rarely may be AR), affect signaling of pro and pre cells. (pro or pre cells are present but no Ab)
- Usually present during 1st 6-12 months

- **findings**:
  1- profound deficiency in B-cells
  2- no lymphoid tissue (no tonsils but thymus normal)
  3- low immunoglobulin in blood (↓ antibodies)
- high risk for infections (strept. Pneumonia, H-influenza B, S- aureus)

ليش ببين بعد 6 اشهر وممكن سنوات ؟ لانه الantibodies اللي من الام بتروح لانو ببلش يقلل الرضاعة الطبيعية والمخزون بروح
ما في ab ← يا zero or very low ← يشخص هيك او انو اعطي IVIG

- They have high risk of having giardiasis and entroviral infections ← chronic enteroviral meningeocephalitis and vaccine associated poliomyelitis (if it eas viral, life attenuated)

- **Treatments**:
  1- antibiotics
  2- lifelong infusion of immunoglobulin:
  - pooled from many individuals
  - gives passive immunity
  - boosted immune system

- **Common variable:** It's heterogeneous disorder

- **Presentation:**
  . Infancy and childhood (but mostly 20-30 yrs) as a first presentation, initial periods of normal immunity then ↓in immunoglobulin
  . With males and females equally

- **Labs:**
  1- Mature B-cell normal in number and morphology (or even low)
  2- But ↓in (B-lymphocyte) plasma cells (failure of B-cells to differentiate), defect in interaction between B & T, mostly causes by T-cell defect (variable T-cell number)
  3- low levels of most or all (Ig) classes
  4- Frequent bacterial infections

- **Pathogenesis :**
  . Defect in gene encoding ICOS (inducible C0-stimulator), CD19, 21, 81 and trans-membrane activator and Ca+2 modulating cyclophilin (TACI) → arrest in plasma cell differentiation
  . Serum IgG < 500 , IgA < 10, IgM low

- **Presentation:**
  1- In young children FTT
  2- Malignancies → B-cell lymphoma
  3- Recurrent respiratory infection → damaged bronchi → bronchiectasis
  4- Autoimmune disease 20% → RA, vitiligo, hemolytic anemia, GI diseases, neutropenia, thrombocytopenia, pyoderma gangrenosum.

- **DDx:**
1. X-linked agammaglobulinemia
2. X-linked lymphoproliferative hypogluboulinemia
3. Hyper IgM syndrome
4. Hypogammaglobulenemia as associated with thymoma 2ndry to medications or protein losing enteropathy

IgA deficiency:

- Common congenital type (autosomal inheritance) → dominant or resesive
- Common 1ry Ab deficiency ← selective IgA → < 10 mg\dL but other types or Ig is normal
- Dx at age of 7 trs → ما بقدر اشخص قبل
- Total IgA deficiency → undetectable IgA in serum or <5 mg\dL
- Partial IgA → ↓ levels more than 2 standard deviation below normal age-adjusted mean.
- Some congenital non-inherited cases associated with TORCH
- Administration of phenytoin, D-penicillamine, sulfasalazine, hydroxychloroquine increases the risk.
- Most of them are asymptomatic with:
  1- celiac 2- food allergy 3- autoimmune 4- recurrent sinopulmonary infections 5- recurrent diarrhea

  انتبه: ممنوع تعطي دم عادي لانه ممكن يكون في IgA بالدم الي رح تعطيه وعنده AB ضدهم فيصير معه anaphylactic shock بالتالي بتعطي free IgA blood.

  Treatment: antibiotics → we don't give IVIg except in certain criteria

IgG subclasses:

- Total IgG levels are normal but one or more of the 4 subtypes is selectively decreased.
- الناس الطبيعيين ممكن يصير معهم قلة بنوع او اكثر عشا هيك مهم اسال عن recurrent infection Hx
- How to Dx? Inability to form AB against protein or polysaccharide antigen (the best) + Hx of recurrent infections and requiring therapy.
- IgG1 → protein antigen (anti-tetanus\diphtheria AB)
- IgG2 → polysaccharide antigen (antipneumococcal) + IgG4 (capsulated bacteria)
- IgG3 → respiratory viruses
- Complement fixation and activation: IgG3, 1, IgM and lesser degree IgG2.

- Transient hypogammaglobulenemia of infancy:
  Temporary condition → delay in Ig production.
- Etiology unknown but thought to be prolongation of physiological type
  → Ig levels remain low up to 1 yr then starts to increase (2-4 yrs) to normal levels (age-appropriate levels)

- **Dx:**
  1- Hx of recurrent sinopulmonary infections
  2- Normal levels of B-cell and I-cell
  3- Normal AB response to protein antigens (tetanus, diphtheria)
  4- Ig levels <200 mg\dL up to 1 yr, then starts to increase

T-cell disorders (combined ID):

- Profound ↓ or absence of T-cell (# or function). + B-cell dysfunction (due to absence of the gene itself or 2ndry to T-cell dysfunction.

DI George syndrome:

- Genetics: 22q11.2 deletion
- Appears in newborn and infancy.

- **CATCH 22 syndrome:**
  - **C**ardiac anomalies, **A**bnormal facies, **T**hymic hypoplasia (may be aplasia), **C**left palate, **H**ypocalcaemia.
  - **22**: gene.
- May have pyogenic infections, partial or complete T-cell dif.
- They have hypoplasia of 3rd and 4th pharyngeal pouches
- Associated with hypoparathyoridism → seizures or mental retardation (mild to severe)

- **Dx:**
  1- fluorescent in situ hybridization
  2- OCR + DNA probe to detect the deletion.

- **Due to hypoplasia in 3rd and 4th pharyngeal pouch:**
  1- Thymic hypoplasia
  2- Parathyroid hypoplasia (neouronal sizures)
  3- Bifid uvula
  4- Dysmorphic features
  5- Esophageal atresia
  6- CHD (ASD, VSD)
  7- Anomalies of great vessels (right aortic arch)

  . **Dysmorphic features:**
  1- Micrognathia
  2- Fish mouth
  3- low-set, large, dorsally rotated ears
  4- Hypetelorism
  5- Short philtrum
  6- Medial cleft → vertical indentation in middle upper lip.

  . **Cardiac anomalies:**
  1- Tetralogy of fallot (common)
  2- Transposition of great vessles
  3- Double utlet Rt ventricles
  4- VSD, ASD
  5- Interrupted aortic arch. (common)

Severe combined ID:

- No adaptive immunity and sometimes natural killers
- **Types**:
  1- X-linked:
  - the most common t50% of severe CID ,
  - only males affected, mutation in Xq13.1 for gamma chain
  - pts don't have T-cell or natural killers but normal # of B-cells
  - Ig are low or undetectable → no CD4 T-cell to stimulate B-cell

  2- Autosomal recessive:
  - defect in Janus kinase 3 (JAK3) which bind to gamma chain.
  - Similar phenotype like X-linked
  - T-cell with normal B-cell and natural killer number.

  3- Adenosine deaminase (ADA) 15%
  4- Purine nucleotide phosphorylase (PNP)

- **Clinical presentation:**
  1- First few months of life
  2- Opportunistic infection + viral (C.albicans, measles, varicella, CMV, EBV, parainfluenza 3)
  3- Severe enterovirus infection (severe diarrhea)
  4- Severe lymphopenia at birth
  5- Graft versus host D. from maternal immunocomplement T-cells crossing the placenta.
  6- Pneumonia, sepsis, otitis media, cutaneous infections.
- No Ig, no lymphoid tissue, small tonsils, small or no thymus

- **Tt** → true pediatric emergency → bone marrow transplant or death by 1 yr of age
  now → recently gene therapy

Ataxia-telangiectasia:

- Usually after 5 yrs not before.
- Autosomal recessive, 2-5 yrs
- High alpha fetoprotein as lab.

- **Characterized by**:
  1- progressive cerebellar ataxia → from beginning of walking, wheel chair at 10-12 yrs
  2- oculocutaneous telangiectasia → start at 3-6 yrs
  3- chronic sinopulmonary D. and bronchiectasis

- **Manifested** as recurrent meningitis, pneumonia, otitis media
- Neurological and endocrine problems especially DM.
- High incidence for malignancy, highly sensitive to ionizing radiation

- ال characteristics و ال alpha fetoprotein
والعمر اكثر من ٥ هيك بقدر اشخص

- قبل ٥ سنوات بعتمد ال ataxia وال clinical

- **By examination:**
  1- tics 2- drooling 3- irregular eye movement 4- mask-like faces

Wiskott-Aldrich syndrome:

- X-linked, in early infancy
- **Manifested** as classical triad:
  - eczema
  - thrombocytopenia
  - susceptibility to opportunistic and encapsulated bacteria.

- Defect in 53-KD protein
  - associated with: small platelets, cellular and humeral immune dysfunction

BE CAREFUL → in T-cell defects, fatal reactions may occur from life attenuated vaccines or BCG.

- **T cell defects:**
  - carry high incidence for malignancy
  - poor survival beyond infancy or early childhood

Complement system:

- Plasma and membrane proteins:
  - innate immune response
  - adaptive immunity

- They can kill pathogens without Abs by opsonization
- It can be activated by 3 pathways : classic, alternative, lectin
- It's disorders can be inherited deficiency or 2ndry to increase in consumption.

- **What indicates defects?**
  1- Recurrent Neisseria meningitis
  2- Angioedema
  3- Severe, recurrent skin and respiratory tract infection
  4- ↑ Incidence of autoimmune D.
  5- Recurrent bacterial infections with extracellular encapsulated organisms → S.pneumonia and H.influenza.

- Deficiencies in early components of classic pathway (C1. , 2, 4):
  Not severe infections, pts may have recurrent encapsulated bacteria and sinopulmonary infections + if young → ear infections

- C1, 2, 3, 4 → high incidence for autoimmune d. especially SLE.

C3 (complete absence):

- pyogenic infections with encapsulated bacteria (H.influenza, S.pneumonia)
- With time ABS are formed so infections become less severe and less frequent.

C5, 6, 7, 8, 9 (terminal complement def.):

- Forms membrane attack complex (foe Neisseria and gram –ve)
- Invasive pneumococcal or meningococcal disease.
- These pts should be immunized against encapsulated organisms.

Congenital C1 inhibitor def. → angioedema

- Recurrent, non-pruritic lasts for 48-72 hrs.
- Happens spontaneously or after minor trauma, anxiety, stress.
- With acute abdominal pain, edema of upper airway (laryngeal edema):
  life threatening and may lead to RS arrest so need emergency tracheostomy.
- May also have extremities swelling.

Constipation

- Infrequent hard bowel movement, painful bowel movement, difficulty in passing the stool
  Or two or less of defecation per week or passing hard stool at least twice weekly

- Very common in pediatrics (f=m) before puberty then f>m

- **Encopresis** (incontinence) : Voluntary or involuntary passage of stool in an appropriate place at least once per month for three consecutive months.
- Developmental age should be more than 4 years

- **Types of Encopresis :**
  1. **retentive** :
  . 65-95%
  . Constipation to overflow inconvenience
  . Result from constipation and fecal impaction

  2. **non retentive :**
  . Without constipation and incontinence
  . No evidence of fecal impaction
  . No anatomic, endocrine, inflammatory, Metabolic, neoplastic explanation
  . Has primary psychological etiology

- **Normal pattern of stooling:**
  Passing meconum in first 36 hours > feeding (more frequently with breastfeed) then start to decrease gradually with age due to :
  1. change in the transient time
  2. pattern of colonic motility
  . In childhood :most of them will have 3 times / day to 3 times /week
  . Generally : regular or normal movements vary among children and infant

- **Constipation :**
  Voluntarily constrict anal sphincter (no evacuation)>stretching of ampulla >water absorbed and become hard stool > with time > overstretched ampulla > decrease urge to defecate > stool pushed to anal canal leading to soiling
-
  Type of constipation :
  1. functional (non-organic) commenest
  2. non-functional (organic)

1-functional: 95%

  . At age of 1 year and older (especially in preschool age)
  . No anatomical or biochemical causes

Criteria to diagnose constipation :

At least 2 of 6 for 1 month in infant and 2 months in children

1-two or less defecation in toilet /week

2-history of painful or hard bowel movement

3-large fecal mass in rectum

4-large stool diameter which may abstract the toilet

5-at least 1 event of incontinence /week

6-history of retentive posture (standing or sitting with legs stiffed, crossed or extended)

**should exclude organic causes .

Functional constipation:

1-depression

2-toilet training issues

3-sexual abuse

4-introducing solid food or cereal

5-developmental (ADHD, Cognitive handicap)

2-organic constipation:

- 5%
- Distinguished clinically(hx and PE)

Acute alarming signs :

1-delayed meconium passage

2-fever, vomiting, diarrhea

3-rectal bleeding and severe abdominal distention

Chronic alarming signs :

1. constipation from birth or early infancy
2. narrow stool diameter (ribbon shape)
3. urinary incontinence or bladder disease
4. FTT or weight loss
5. family history or hirschsprung disease
6. congenital anomalies or extra intestinal manifestation

Possible organic causes :

1. celiac
2. milk protein allergy
3. hirschsprung
4. anal sphincter or stenosis
5. neuronal dysgenesis
6. pseudoobstruction
7. collagen vascular disease
8. rectal abscess or fissure
9. stricture after NEC
10. anterior dislocation of anus
11. cystic fibrosis
12. dehydration
13. hypothyrodism
14. spinal cord lesion
15. drugs

Hirschprung disease:

No ganglion cells associated with septal defect and Down syndrome

S and S :

1-FTT or delay growth

2-delayed meconium passage

3-vomiting

4-abdominal distention

5-tight anal canal with empty ampulla

6-squirt sign: post rectal exam:explosive expulsion of stool

Defenitive diagnosis by biopsy: absence of gangilion cell in submucs plexus

How to approach patient with constipation?

1-history : Any difficulty in defecation, regularity, hard or not, pain, FTT, soiling, feeding, time of passing meconium, toilet training history, family history, drug history, sexual abuse

Common with holding behavior (To avoid pain during defecation) :

1. squatting
2. stiffing
3. crossing leg
4. holding onto mother or furniture
5. flushing, sweating, crying

Functional :

1. more than 2 years
2. have Encopresis and abdominal pain with toilet training and negative family history
3. very large stool size
4. no FTT
5. no enterocolitis

Hirschprung :

1. at birth or less than 1 year
2. have pain without Encopresis
3. family history but not always
4. small, ribbon like stool
5. FTT
6. possible enterocolitis

- **Always exam the back for dysraphism and lower limb tone, strength**

In rectal examination :
Size of anus, any skin changes, impacted stools, if there is expulsive expulsion of stool, anal wink > if negative >neurological disease .

When the patient has warning signs or failed to response to management do detailed investigation

When to do abdominal x-ray?

1. inadequate Hx
2. if he is obese or limited examination or physical examination not done

Barium enema :
Unprepared patient, if we find suggestive finding in physical examination, or early onset constipation

Findings :

- Functional :massive stool amount, no transitional zone
- Hirschsprung : transitional zone, delayed evacuation of enema >24

- Not good in first month of life > transition zone need time to develop
- No rectal manipulation before 48 years (ممكن يوسعوا القولون), no air,contrast enema

Spine radiography :
- lumbosacral if evidence of dysraphism or neuro impairment

- If high suspicion of neurological dysfunction do MRI to exclude:

1. cord tumor
2. tethered cord

Investigation:

Only if there is suspicion

1. celiac > TTG, CBC
2. thyroid >TSH, T4
3. electrolyte and calcium
4. lead level
5. urine analysis (if impaction in rectosegmoid)

Motility testing :

If negative signs for organic causes and no response to management of function

1. **colon transient study**

- Not helpful in routine evaluation
- Use radio opaque marker (sitz mark capsule)
- Should remove fecal impaction and stop laxatives before days of the study

2. **anorectal monometry**

- Placement of catheter that measures neuromuscular function
- It measures : Sensation, inhibitory reflex, compliance, squeeze pressure

- **functional : internal sphincter relaxation
- Hirschsprung : no relaxation

Management:

1-disimpaction

2-maintenance therapy (prolonged laxatives and behavioral therapy)

3-dietary changes (increase fiber)

4-gradual tapering (withdrawal of laxatives as tolerated)

Disimpaction:

1-oral

2-rectal

- If history of perineal trauma
- Difficulty in tolerating enemaor history of painful defecation

a. **polyethylene glycol 3350**
   - 1-1.5 g/kg/day up to 6 days
   - Dissolve daily dose in 10 ml/kg water

b. **polyethylene glycol with Electrolytes solution (Golytely)**
   - 25ml/kg/hr

- Maximum 1000 by NG tube
- Or 20ml/kg/hr for 4 hrs per day

c. **mineral oil**
- 3ml/kg/day orally
- Not used in infant or neurological impaired children due to high risk of pneumonitis >due to GERD

Other agent :

Lactulose, sorbitol, senna, bisacodyl, magnisum hydroxide, magnisum citrate.

- Oral and rectal are more effective in moderate to severe impaction

Rectal :for patients with severe impaction.
We use sodium phosphate enema or mineral oil with sodium phosphate

1-**sodium phosphate :**

- 33ml (2-5y)
- 66ml(5-12y)
- 133ml(>12y)
  If necessary repeat within 12-24 hrs

2-Saline : 10-15ml/kg

3-bisacodyl suppositories: glycerin for infants and bisacodyl for older

4-mineral oil:

- 66m(2-12y)
- 133ml(>12y)

Side effects :

- Enema in general >risk for trauma
- Normal saline >abdominal cramp
- Hypertonic phosphate >cramping, with high risk of hyperphosphatemia, hypokalemia, hypocalcemia
  Dont give in children <2yrs
- Senna >cramping
- Mg phosphate >hypermagnusemia
- Bisacodyl >both tablets and suppositories >cramping, Hypokalemia, diarrhea
- Polyethylene glycol >should admit the patient to the hospital
  He needs NG tube, large volume of solutions,
  SE : nausea, vomiting, cramping, bloating, aspiration

Maintenance therapy : 1-laxatives 2-behavioral changes

1-laxatives : After disimpaction to retain the bowel and avoid re-impaction

- **We use** : Lactulose, mineral oil, magnisum hydroxide, polyethylene glycol 3350
- Parents can adjust the dose according to the response
- Encourage the child to use toilet 5-10min/day at least 3 times at the same time

(جدول سلايد ١٠ السلايد الثاني)

- Choosing the dose should be based on age, weight, severity

2-behavioral changes :

- Toilet training 5-10min/3 times daily
- Reward system
- Monitoring the child food, drugs, stool incontinence

Dietary changes :

1. high diet fiber or fiber supplement
2. no clinical significant of fluid intake unless he is dehydrated

If the child unresponsive to other measures with atopic symptoms we suggest a trial of at least two weeks to stop cow milk

Discontinuation of laxatives :

- Goal of therapy: Normal stool caliber every 1-2 days without incontinence
- Once we achieve the goal we can start to decrease the dose , But wait at least 6 months before decrease

Failure of treatment :

1. inadequate medication
2. premature discontinuation

If repeated failure? Reconsider your diagnosis

Surgery :

Anal sphincter (internal) relase > by myomectomy or injection of botulism toxin

Hemoglobinopathy

Alpha globin : Symptomatic in utero and after birth

Beta globin : Asymptomatic until 3-9 months when HbA replace HbF

Sickle cell: Valin instead of glutamine in the 6th position in beta globin

Sickle cell anemia :

- HbS in 90% of total Hb
- Homozygous :both beta globin have sickle Mutation

Sickle cell disease :

- Not only anemia (HbS with other Mutation) >HbC or Thalassemia
- Heterozygous :HbS >50% of Hb
- RBC less than 20 days (lifespan)

Intravascular sickling:

- Happens in post capillary venules, by increase the obstruction (by sickled RBC) and increase adhesion (between RBC, WBC, and vascular endothelium)

Sickle cell disease :

- Inflammation based on non-specific markers
- Increase cytokines, and increase baseline WBC count
- Should do newborn screening >if positive start penicillin before 4 months of life

Commenest diagnostic methods :

1. high performance liquid chromatography (HPLC)
2. thin layer isoelectric focusing

- If the initial test is positive >retest in the clinical visit then after 6 months of age to determine the final phenotype
- Cardinal features of SC anemia > acute vaso-oclussive pain

If you suspect osteomyelitis think of S. Aureus or salmonella

When to admit febrile sickle cell child?

1. capillary refill >4 seconds (poor perfusion)
2. hypotension :systolic <70 if 1yr or less, or less than 70+(age*2)
3. dehydration
4. severe pain
5. Hb <5g/dl
6. 7-on CBC :
6-temperature >40
8--plt <100,000
9--wbc >30,000 / <5000
10-hx of pneumococcal sepsis

Aplastic crisis :

- Parvovirus 19,fever and reticulocytopenia, treatment conservative
- Give RBC if Symptomatic or concurrent illness like acute chest syndrome
- May also associated with pain, spleen sequestration, stroke, GN

Splenic sequestration :
Life threatening
May happen at age of 5 w but usually 6 months - 2yrs

Clinically :

1. left abdominal pain
2. rapid splenomegly
3. Hypovolemia
4. decrease in Hb at least 2g/dl
5. anemia with Hb less than 2g/dl
6. reticulocytosis + thrombocytopenia
   triggered by fever, viral infection, bacteremia

Treatment :

- Isotonic fluid or 5ml/dl to maintain stability and treat Hypovolemia
- Blood transfusion that will cause elevation in Hb >10 > hyperviscosity syndrome
- 2/3 will experience recurrence within 6 months
- To prevent future events >prophylactic spleenectomy in acute episode

Sickle cell pain (hand foot syndrome) :

- Dactylitis
- First manifestation of pain in 1st 2 yrs (acute vaso-oclussive occlusive pain)
- Pain is unremitting, affect any part but mostly chest, abdomen or extremities
- Usually they experience at least 1 episode per year
- They will have both hemolysis and vaso-oclussive events

Acute :

- Aplastic crisis
- Acute chest syndrome
- Stroke
- Priapism
- Hematuria (papilary necrosis)
- Splenic sequestration
- Bacterial sepsis or meniningitis
- Recurrent vasoclussive pain
- (MS or abdominal pain, dactylitis)

Chronic :

- Anemia and jaundice
- Spleenomegaly and functional asplenia
- Caedimegaly and functional murmur
- Protienemia
- Hyposthenuria and enuresis
- Avascular necrosis
- Pulmonary HTN
- Cholilithiasis
- Delay growth and sexual maturation
- restrictive lung disease
- Leg ulcers and hemosidrosis
- Proliferative retinopathy

Clinical manifestation :

- Fever and bacteremia:
  Fever is an emergency need direct medical evaluation and antibiotics because it is indicate infection (high mortality rate)

- Infant with sickle cell anemia at 6 months > abnormal immune function due to spleen infarction
- At 5th year they will have complete functional asplenia

- Be aware of encapsulated organism :
  S. Pneumonia
  H. Inf (B)
  N. Meningetidis

Treatment

Depends on the risk of occult bacteremia

- High risk > admission, IV antibiotics, observation
- Moderate risk >in emergency room give 3rd generation cephalosporins
- No risk>give the antibiotic in outpatient clinic

If you treat with ceftriaxone observe your patient, why?

May have life threatening immune hemolysis (sever, rapid)

Neurological complication:

It varies from silent abnormalities found on imaging to stroke with deficit

- Focal stroke: overt neurological deficit >24hrs +/- abnormal imaging of the brain (infarction in T2 MRI) related to the deficit
- Seizure, headache, cerebral venous thrombosis, reversible posterior leukoencephalopathy syndrome
  Management :treat the stroke

1. Oxygen (O2 sat >96%)
2. transfusion within 1 hour to increase HB maximum 10g/dl

- Do exchange transfusion less in acute stroke attack?
  Risk for stroke attack better than transfusion

- Do head CT to rule out cerebral hemorrhage

- Brain MRI with diffusion weighted imaging to distinguish infarction from PRES

- Transcranial doppler U/S:
  Use as a primary prevention of overt stroke

Assess :

1. terminal portion of internal Carotid
2. proximal of middle cerebral artery

- SC anemia patient with elevated time velocity >200cm/sec >>>increase risk for CVA
- 180-200 cm/sec >>> threshold
- Should repeat it within few months
- Primary approach to prevent recurrent strokes>>blood transfusion
- The aim? Keep HBS <30%

Pulmonary complications :

Second most common cause of admission with high mortality

Acute chest syndrome : life threatening condition

How to **Dx?**

New radiodensity on X-ray with 2 of the following:

1. fever
2. hypoxia
3. cough or chest pain
4. respiratory distress

Renal disease and ensuris : (7 disease (على عدد احرف disease))

Major comorbid that cause premature death

1. pyelonephritis
2. papilary necrosis
3. infarction
4. Nephrotic
5. gross hematuria
6. hyposthenuria 7. renal medullary carcinoma

   Clinical presentation : 1-Hematuria 2-Protienuria 3-Renal insufficiency 4-HTN 5-Concebtrating defects

Cognitive and psychological complications :

- Retinopathy
- Leg ulcers
- Delay onset of puberty

Hydroxurea :

Myelosuppresive agent, it reduces the frequency of pain attack, the rate of ACS and transfusion up to 50%

- We start with 15-20 mg/kg once / day
- After 8 weeks we increase 5mg/kg on the initial dose
- Maximum dose 35mg/kg per dose
- Therapeutic effect may need several months:

1-decrease in TCD velovicity

2-increase in total AB level

Hematobiotic stem cell transplantation :

The only cure with HLA matching

When to transplant?

1. stroke
2. abnormal TCD
3. recurrent ACS

RBC transfusion :

If he has :

1. ACS
2. acute stroke
3. aplastic crisis
4. splenic sequestration
5. pre surgery to prevent ACS
6. first attack of stroke in patient with abnormal TCD or MRI findings (silent stroke)

Radiological findings :

1. single lobe involvement (lt Lower), or multiple lobes (noth lobe)
2. pleural effusion (uni or bilateral

- Develop rapidly from single infiltrate to extensive +effusion

Etiology :

1. fat necrosis due to infarcted bone marrow
2. infection, but only 30% have positive culture to s.pneumonia,chlamydia, mycoplasma

-Best managment to prevent the progression :transfusion

How it happens with sickle pain?

The patient start feeling of chest pain so he take opioid (The best is Morphin, then less in nalbuphine and hydrochloride) so he will develop hypoventilation ACS

How to prevent this?

Regular use of incentive spirometer (10-12 breath /2hrs)

When to transfuse blood in ACS?

1. decrease in O2 sat
2. increase work of breathing
3. decrease in hemoglobin 2g/dl below the baseline
4. history of ACS that need ICU
5. rapid changes in respiratory effort +/- changes on X-ray

Diagnosis :

1. CBC and chemistry (for diagnosis and daily for monitoring)
2. CXR
3. blood culture
4. pulse oxymeter (continues)

Treatment :

1. O2
2. transfusion (exchange or mixing)
3. antibiotics (3rd cephalosporins and macrolids)
4. fluid and pain control
5. incentive spirometry
6. chest physiotherapy

<u>Methods of transfusion :</u>

1. automated erythrocytopheresis

2. simple transfusion
   1+2 :minimum net iron after transfusion

3. manual exchange transfusion (phlebotomy of set amount of patient blood followed by rapid administration of donated packed RBC) /least preferable in regular transfusion (chronic patients) because net iron is higher than other methods

But erythrocytopheresis is <u>not</u> that frequently used because:

a. large venous access
b. need expert
c. multiple units of matched RBC
d. need available machines

Toxicity is due to iron after 10 transfusions

Monitored by :

1. serum ferritin
2. liver MRI and heart (most accurate)

Treatment of excessive iron by chelating agents:

- Defroxamin SC
- Deferasirox orally *2

We give prophylactic penicillin

Functional abdominal pain

- Common cause for chronic abdominal pain

Characters :

1. continuous for more than 3 months or recurrent intermittent for more than 3 months
2. should exclude all other causes
3. can't be explained by any abnormalities even with full history, examination and testing
4. no serious or identifiable underlying cause

- Affects 10% of children at age between 7-12 years
- Triggers varies but nerve signal or chemical by gut or brain can increase in sensitivity of the gut to trigger the pain such as stretching or gas bloating (normally they don't cause pain)

Risk factors :

1. physical or emotional traumatic experiences and preceeding history of GI infection
2. history of anxiety, depression or any psychatric disorders (will have exaggerated pain)

- FAP infrequently may affect appetite and sleep

FAP vs IBS :

FAP :

- Almost daily (worse at morning)
- No relation to meal
- Not relived by defecation
- Result from stress
- Prevent or delay children from attending school

IBS :

- Onset of pain at time of stool changes frequency and consistency
- Stool (diarrhea and constipation)
- Relieved by defecation
- Related to gut motility

Functional abdominal pain :

Must include all : at least 1/week for 2 months

1. episodic or continous pain
2. insufficient criteria for other diseases
3. no evidence of inflamatory, anatomic, Metabolic or neoplstic process that explain the symptoms

Functional abdominal pain syndrome :

- **Must have at least 25% of the time with one or more for two months and at least once/week**

1. loss of daily functions
2. somatic symptoms :headache, limb pain, difficulty in sleeping

Irritable bowel syndrome :

At least 1/week for 2 months

Must include all of the following :

1. abdominal discomfort (not pain) or pain with two of the following :
   A. improve with defecation
   B. onset with changes in stool frequency
   C. associated with change in form (appearance)
2. no evidence of inflamatory, anatomic, Metabolic or neoplstic process that explain the symptoms

Abdominal migraine :

Must include all of the following :

1. pain interfere with activity
2. two or more times in the last 12 months
3. paroxysmal intense, acute periumbilical pain for 1 hr or more
4. intervening periods of usual health lasting for weeks to months
5. pain associated with 2 or more of :
   Nasua, vomiting, headache, anorexia, pallor, photophobia
6. no evidence of inflamatory, anatomic, Metabolic or neoplstic process that explain the symptoms

Recurrent abdominal pain :

- Affects 10-20% of school age children
- Most of them due to psychological causes not organic
- central, vague pain
- Frequency and severity not related to the etiology

Some of **organic causes :**

1-H.pylory : Dx by urea breath test, rapid urease test, histology

2-eosinophilic esophagitis, reflux esophagitis

- Epigastric pain associated with young infant
- It's improved upon introduction of solid food and on erect position
- Symptoms developed around 2 yrs
- May happen with obesity, overeating, and sedentary lifestyle , **Dx** by biopsy (allergy)

3-carbohydrates intolerance :

- Main one is lactose in mammalian milk
- Insidious onset, happens after hours of milk ingestion, flatulence, diarrhea
- Dx by withdrawal and challenge test

4-familial mediterian fever :

- Mutation in short arm in chromosome 16
- Abdominal pain, myalgia, fever, joints pain, chest, skin like cellulitis, plueral, pericardial

Peritoneal symptoms :

- Almost all patients have pain and may progress to peritonitis
- Associated with seronegative spodyloarthritis

Complication : amyloidosis > present with proteinuria > Nephrotic syndrome and death due to renal failure

By examination : Splenomegaly, high grade fever, changes in joints, rash, tender muscles

5-inflamatory bowel syndrome :

- Vague pain, loss of appetite, fever, diarrhea, failure to thrive, poor weight gain, arthralgia, poor pubertal development

6-surgical procedure conditions (acute) :

- Intussuscption, meckel diverticulitis, intestinal malrotation, lymphoma, choledochal cyst

Red flag : indicate organic causes :

- Vomiting, weight loss, FTT, nocturnal diarrhea, emesis or blood in stool, abnormal baseline investigation, night-time awaking from pain, dysphagia, arthritis, perineal disease, FHx, delayed puberty, bilous emesis, pain in site other than periumbilical

- Nausea rarely indicate organic causes but vomiting does

Approach to FAP :

By Hx :

1. periumbilical or in multiple sites, headache
2. morning pain, improve in afternoon, and become severe at bed time
   - Hallmark is school absenteeism but organic causes attend school
   - Look for separation anxiety and stress
3. on abdominal examination, distract the child, the pain will disappear

How to approach?

- By Hx and examination > red flags positive > do more investigation to exclude the cause

- If nothing is significant > do baseline investigation :CBC, ESR, amylase, lipase, urine analysis, abdominal US... If normal > it is FAP

- Then **managed** by :

1. Cognitive behavioral therapy
2. antispasmodic, acid suppressant
3. high fiber diet
4. we may advice them with lactose free diet and probiotics
   بس فعليا فيش اشي مثبت كلها من ال(practice)

DKA

- Complex of Metabolic state (hyperglycemia, ketosis, acidosis)
- Happens at time of Dx of DM type 1 and mostly in young children
- Mortality rate : 2-5%

Who are at high risk for DKA?

1. new onset of type 1 DM if not dx
2. known case of DM 1 if :

- insulin injection is omitted or not enough doses
- intercurrent illness :
  The insulin requirement increases due to high concentration of counter regulatory or stress hormones (glucagon, catecholamine, growth hormon)

- Most common cause of acute illness is **URTI, UTI**
  Or **drugs** :lithium, cocain, clozapine

Pathophysiology :

Inadequate insulin cause :

1. increase fatty acid oxidation > ketone bodies > acidosis > hyperkalemia(renal loss) and phosphate loss in renal
2. gluconeogenesis
3. glycogenolysis and decrease Peripheral glucose uptake > hyperglycemia > osmotic diuresis > renal NA loss + dehydration >decrease tissue perfusion > increase lactate > acidosis > acidosis will cause vomiting and high loss of insensible fluids >increase dehydration

Changes:
Electrolytes abnormalities happens due to renal loss and transmembrane alternation because of the acidosis

1-potassium level :

- Depend on the duration of Ketoacidosis
- At time of diagnosis you found it decreased, normal or increased
- But always you find the intracellular low, how?
  A. When Ketoacidosis happen there will be increase H+ so there will be exchange of potassium intracellularly for H+
  So it hyperkalemia at early stage
  B. then the kidney start to excrete it (clearance) so it will cause transient normal or Hypokalemia

لو طلع hypo معناها ال total body potassium قل كثير

2-phosphate level :
Hypophosphatemia due to renal clearance to eliminate H+

3-sodium level :
Hyponatremia (common) due to renal loss by diuretic effect (osmotic diuresis) and from vomiting (GI loss)

Clinical approach :

1-history :

- Insidious onset
- Symptoms of DM (polyuria, polydepsia, polyphagia, wt loss)
- Symptoms of DKA (fever, fatigue, symptoms of any infection, abdominal pain, nasuea, +/-vomiting)
- If the patient dx with type 1 DM
- If he is at age of puberty
- Most of these symptoms are not specific specially in young children but need high index of suspicion to dx

2-examination :

1. signs of dehydration (delays capillary refill, hypotension, sunken eyes....)
2. tachycardia
3. hypo/hyper thermia
4. kussmal breath (rapid deep)
5. acetat odor (fruity odor) > Metabolic Acidosis
6. abdominal tenderness (peritonitis) or distention
7. sign of infection (UTI, Pneumonia.....)
8. lethargy, or may be coma

Evaluation, it is an emergency!!

by history and examination if you can find the cause then assess the stability of the patient

(Ketoacisosis volume, dehydration degree, Electrolytes abnormalities)

Then

1-two large bore cannula and glucocheck

2-blood sample (BUN, bicarbonate, Electrolytes, serum ketone, sugar)

- **High BUN** in dehydration
- **Bicarbonate** <15meq/l
- **Sodium** (high or low depending on water loss)
- And insert **catheter** to monitor urine output
- And **urine sample** for ketone and sugar
- And **analysis for UTI**
- Also **blood sample** for infection screening (CBC, CRP, blood culture)
- Also **CXR**

3-ABG to assess acidosis severity

- High anion gap
- PH below 7.30

4-fluid replacement with management of hyperglycemia and disturbance of Electrolytes

- Criteria for Dx of DKA :

1. blood glucose >200mg/dl
2. PH<7.35(acidosis)
3. positive ketone bodies >5mmol/l
4. bicarbonate <15meq/l

- Severity assessed by VBG

- Degree of DKA :

Mild : Co2 15-20, PH 7.35-7.25, clinical :only fatigue

Moderate : Co2 10-15, PH 7.25-7.15, clinical :kussmal, oriented but sleepy and aroused

Severe : Co2 <10, PH <7.15, Clinical :kussmal or depressed respiration, and may be comatosed

Note :most serious complication is brain edema and herniation

1-Dehydration correction (cornerstone) : depending on the sodium level

- If sever hypovolemia : give bolus normal salibe 10-20ml/kg
- NS for first 4-6hrs then shift to 1/2 saline

Low sodium :

- Consider 10% dehydration
- If <150meq/l correct over 35-48 hrs
- If <170meq/l correct over 72-96hrs
- Use 0.45 NS as initial solution

High sodium :

- 0.9 saline (250-500)
- Depending on Hydration state
- Or calculate maintenance and deficit then sodium correction
  (Desired _ actual) *wt*0.6 correct ober 24 hrs

- Initial IV bolus of glucose free fluid (no oral fluid in first 36 hrs)>>high risk for aspiration
- Bolus+maintenance +deficit to avoid rapid shift in serum osmolality

How to calculate maintenance?

- **Fluids :**
  - 1st 10kg > 100ml/kg
  - 2nd 10kg > 50ml/kg
  - Rest kg > 20ml/kg
- **Sodium :**
  - 2-3meq/kg

How to write the order?

- 800 ml of 0.45 saline over the first 8 hrs then repeat 800 ml of 0.45 of saline over the next 16 hrs (باعتبار انو المجموع الكلي ١٦٠٠)
- Ongoing loss that result from osmotic diuresis don't need to be replaced unless there is sign of hypo perfusion or large amount loss
- Diuresis usually minimal when serum glucose low (<300 mg/kg)

2-hyperglycemia :

- Regular insulin as continuous IV infusion (0.1 U/h)
- Decrease rate no faster than 100 mg/dl/h to avoid cerebral edema
- When glucose reach 200-250 add glucose to the fluid
- No change in insulin dose before acidosis correction

3-acidosis :

Bicarbonate : give only if

1. PH<7
2. Unstable patient
3. symptomatic hyperkalemia

- PH>6.9 no HCO3
- PH<6.9 give HCO3, gibe 100 mmol in 400 ml h2o + 20meq kcl
- Infusion for 2 hrs
- Repeat every 2 hrs until PH>7
- Monitor K every 2 hrs

Correction :

- Insulin > decrease in production of free fatty acid and protein catabolism
- Enhance glucose use in target tissue

Potential adverse effects :

1. paradoxical increase in CNS acidosis by increase CO2 in BBB
2. shift in oxyhemoglbin dissociation curve cause tissue hypoxia
3. abrupt osmotic changes, increase risk of cerebral edema
4. Electrolytes imbalance :

- Regardless of potassium level at presentation, there is K depletion
- It ms level decrease rapidly then with insulin and improvement of acidosis it is exchanged for intracellular H+

So when to replace?

Potassium :

- K<3.3meq/l, high insulin >>> 20-30 units K >3.3
- K :3.3-5.2meq/l>>20-30/l of IV fluid so K =4.5 level
- K>5.2 dont give Kand check its level every 2 hrs

Potassium : establish adequate renal function (output ~50ml/hr)

- Should be given as 50% KCL, 50% potassium phosphate
- Combination provide the replacement but excess may precipitate hypocalcemia

Complication and follow up :

Monitoring :

- Initial lab : glucose, sodium, potassium, CL, HCO3, BUN, CA, Creatinine, Ph, MG, ABG or VBG, urine analysis
- Serum glucose every 1 hr during therapy
- Assess neurological ans mental status frequently
  (headache, change in mental status > possible cerebral edema)

Complication :

1. cerebral edema
2. Hypokalemia
3. ARDS
4. thrombosis
5. acute circulatory failure
6. DIC (rarely)

- **Cerebral edema** :1-5%of DKA cases
  The most serious one with high Mortality rate
  Happens 6-12 hrs after the start of therapy (after clinical improvement period) due to osmolar shift of fluid and accumulation in the brain

Indicative symptoms :
Change in alertness, vomiting with sudden sever headache

Signs of advanced CE :
Apnea, seizure, papilledema, HTN, bradycardia, pupillary dilation or inequality

Factors correlate with high risk of CE :

1. high initial BUN (sever dehydration)

2. low initial PCo2 3.new onset DM
5. younger than 5 yrs
6. failure of NA level to increase as glucose level decrease during management
7. treatment with HCO3 (no role in DKA) >> except in the previous conditions

So how to manage CE :

1. rapid use of IV mannitol
2. intubation +hyperventilation
3. may requires the use of subdural bolt

Hypokalemia :

- As acidosis is corrected, K will enter the cell so will have fall in K level in spite of large K replacement
- Increase or decrease in K will cause arrhythmia which may be fatal

ECG changes :

1. slight peaked P wave
2. Sligh prolonged PR interval
3. ST depression
4. shallow T wave
5. prominent U wave

- No K bolus as it cause cardiac arrest
- K may cause RDS due to muscle dysfunction

How to manage?

- Don't give K until you know its level
- Once you know the level and voiding is observed (urine output), and after first hour of fluid, all IV fluids should have 20-40 meq/l of K+

If the K level initially normal or high? Wait until it starts to decrease then give K

When to transfer the patient to the ward?

1. acidosis correction
2. tolerate oral feeding
3. discontinue insulin
4. start SC insulin :

- First dose should be given 30-45 minutes before the discontinuation of insulin, then in the ward adjust the dose over 2-3 days (fast acting)

Insulin doses :

If newly onset DM : start with tital daily dose of :

-prepubertal : 0.7u/kg/24hrs

-adolescent : 1u/kg/24hrs

Using any number available in insulin combination

If already Dx : restart the previous doses if they were adequate

Transition to SC insulin :

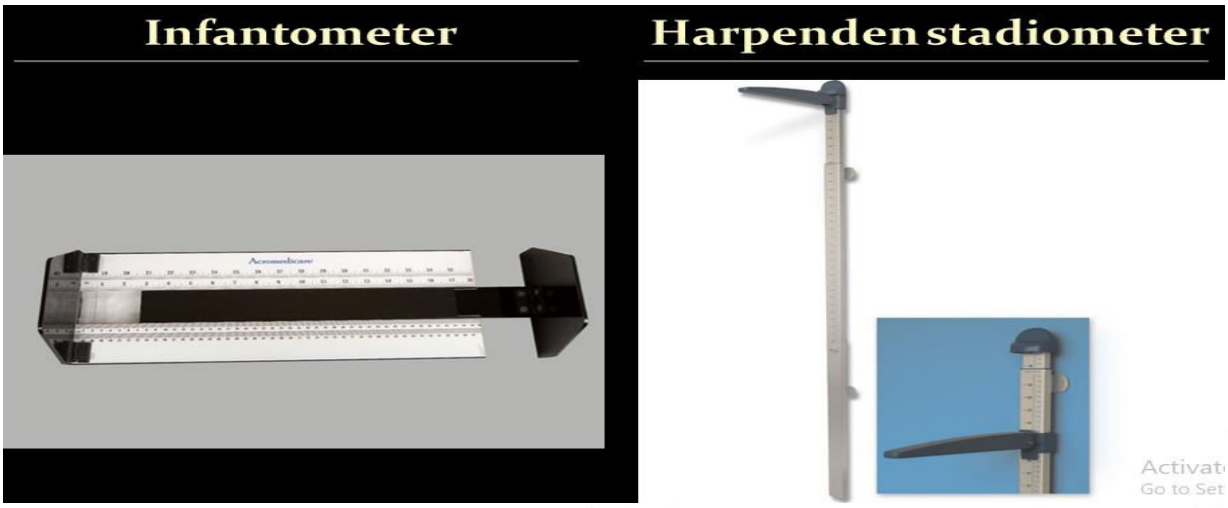
- Fast acting after meals, and large or basal acting at bed time
- This (multiple daily injection) is flexible but requires the patient to inject himself many times and calculate the carbohydrates

Alternative:

- Fixed mixed split dosing regimen with 2 daily injection :
- 2/3 of total at morning (2/3 intermediate, 1/3 fast acting)
- 1/3 at the evening with dinner (1/2 intermediate, 1/2 fast acting)

Short stature

Length VS Height:



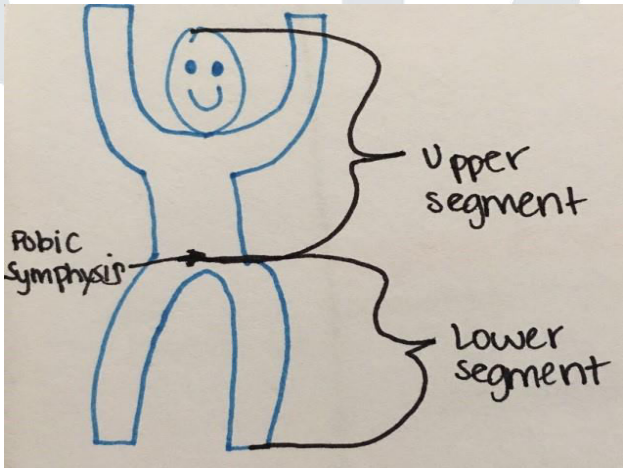
Length (Normal growth):

- Expected height = (6X+77) cm, X = age in years.
- Birth length: 50 cm.
- 3 months: 60 cm.
- 9 months: 70 cm.
- 1 year: 75 cm.
- 2 years: 90 cm.
- 4 years: 100 cm.
- 13 years: 150 cm.

Mid- parental height

✓ <u>For boys:</u>

MPH = (Father's height + mother's height + 13) /2 cm
= (Father's Height + Mother's Height + 5) / 2 in



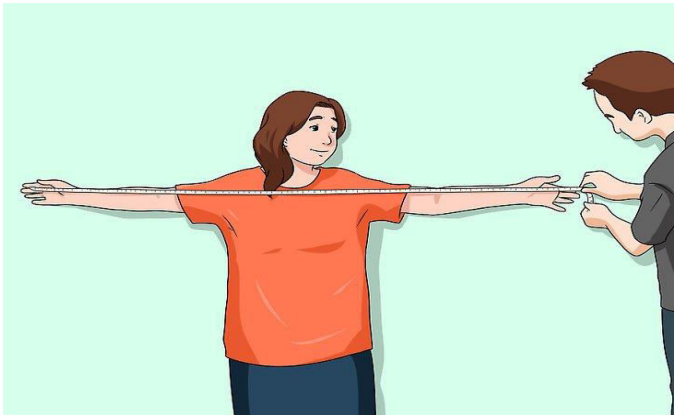
✓ <u>For girls:</u>

MPH = (Father's height – 13 + mother's height) /2 cm
=(Father's Height - 5 + Mother's Height) / 2 In

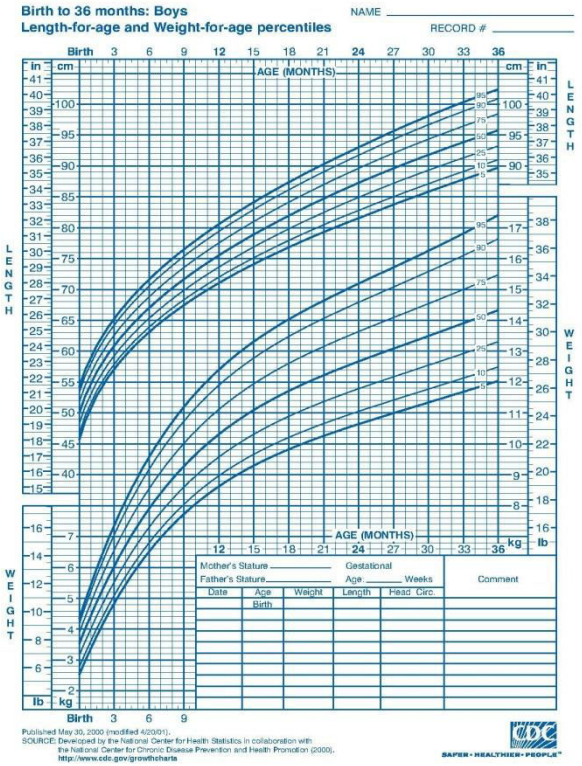
Upper:Lower segment ratio

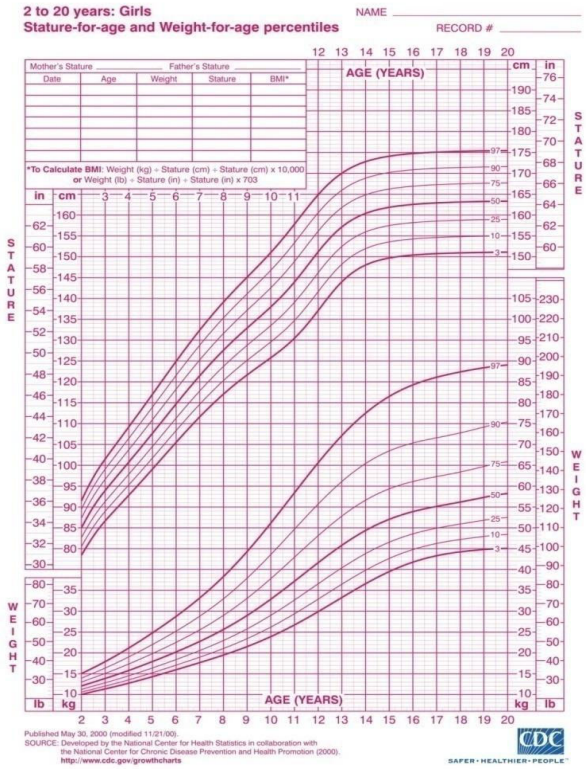
- At birth➔ 1.7:1
- 3 years ➔ 1.3:1
- At 7 years ➔ 1:1

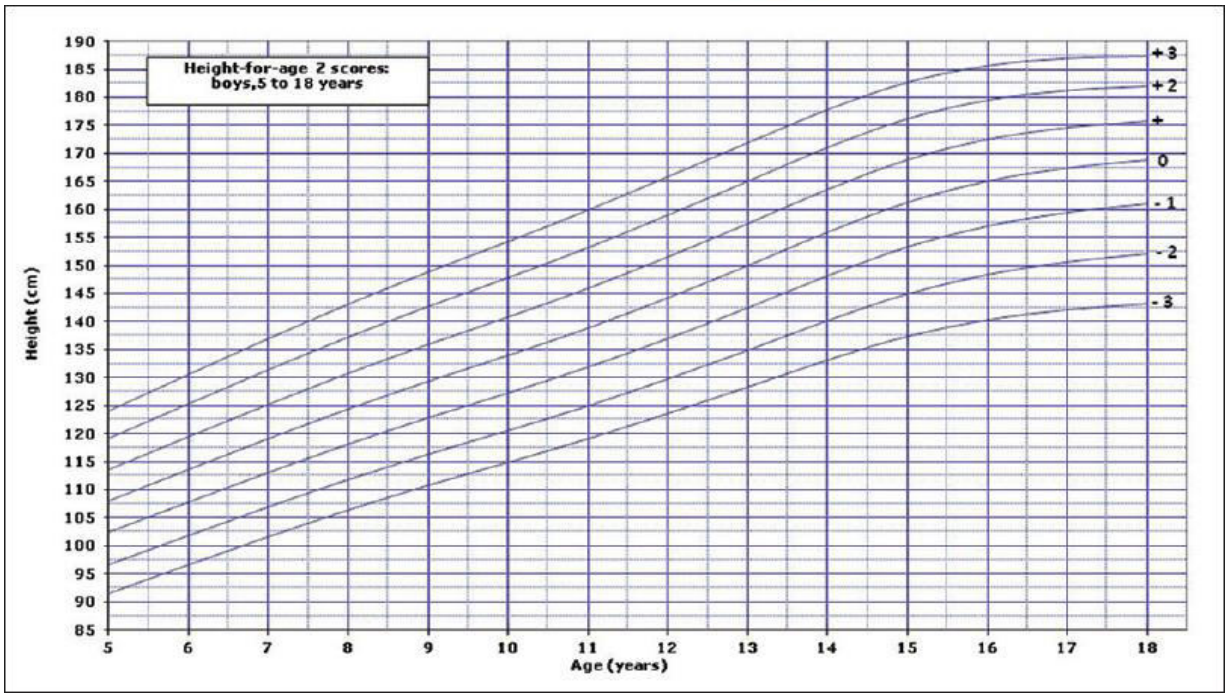
Arm span



Growth chart

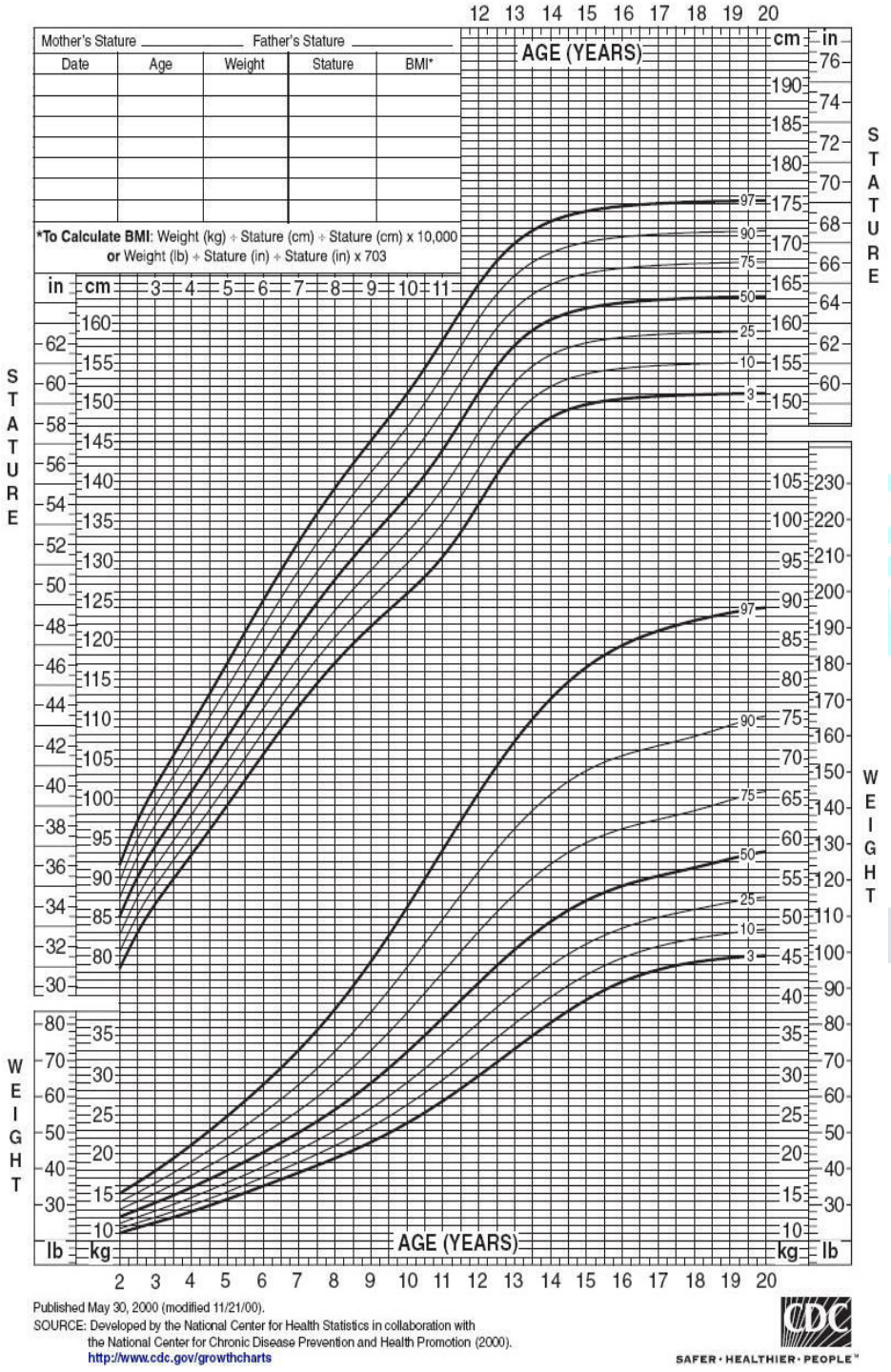




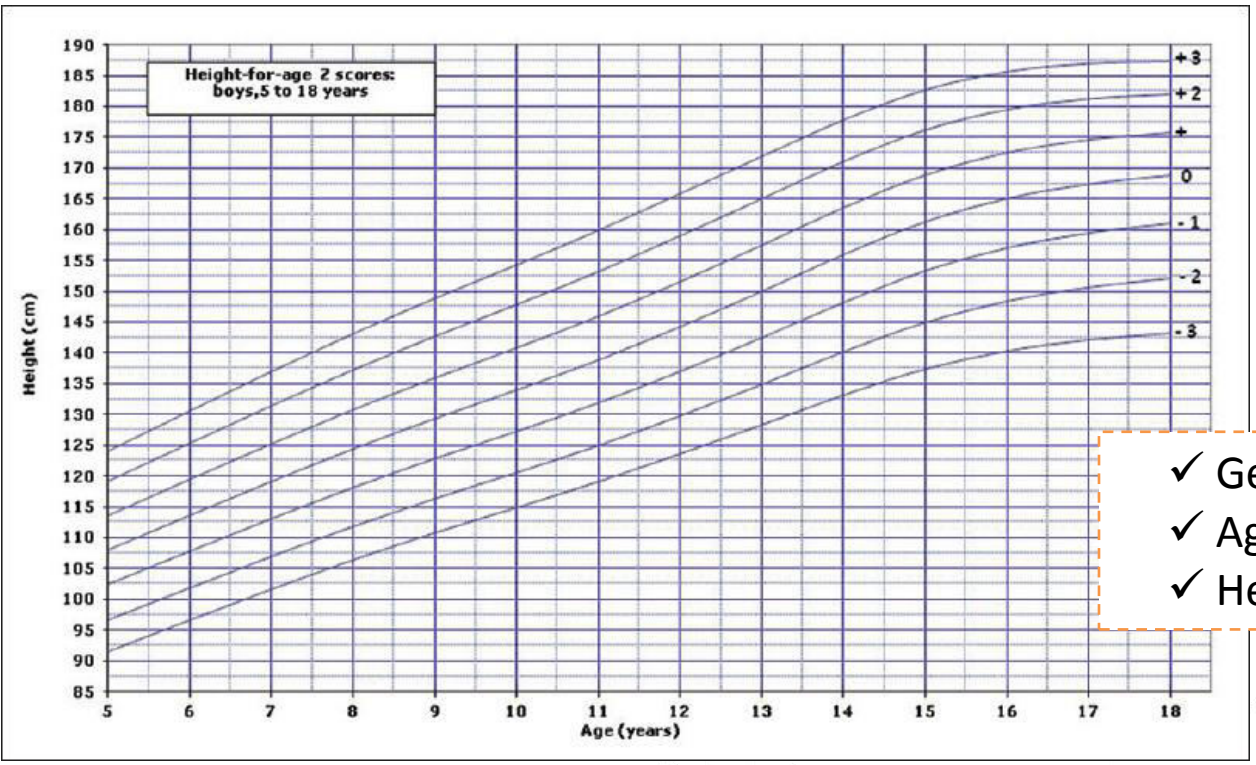


Short stature

- Height below 3rd percentile or less than 2 standard deviations below the median height for that age & sex according to the population standard.
- Or even if the height is within the normal percentiles but growth velocity is consistently below 25th percentile over 6-12 months of observation.

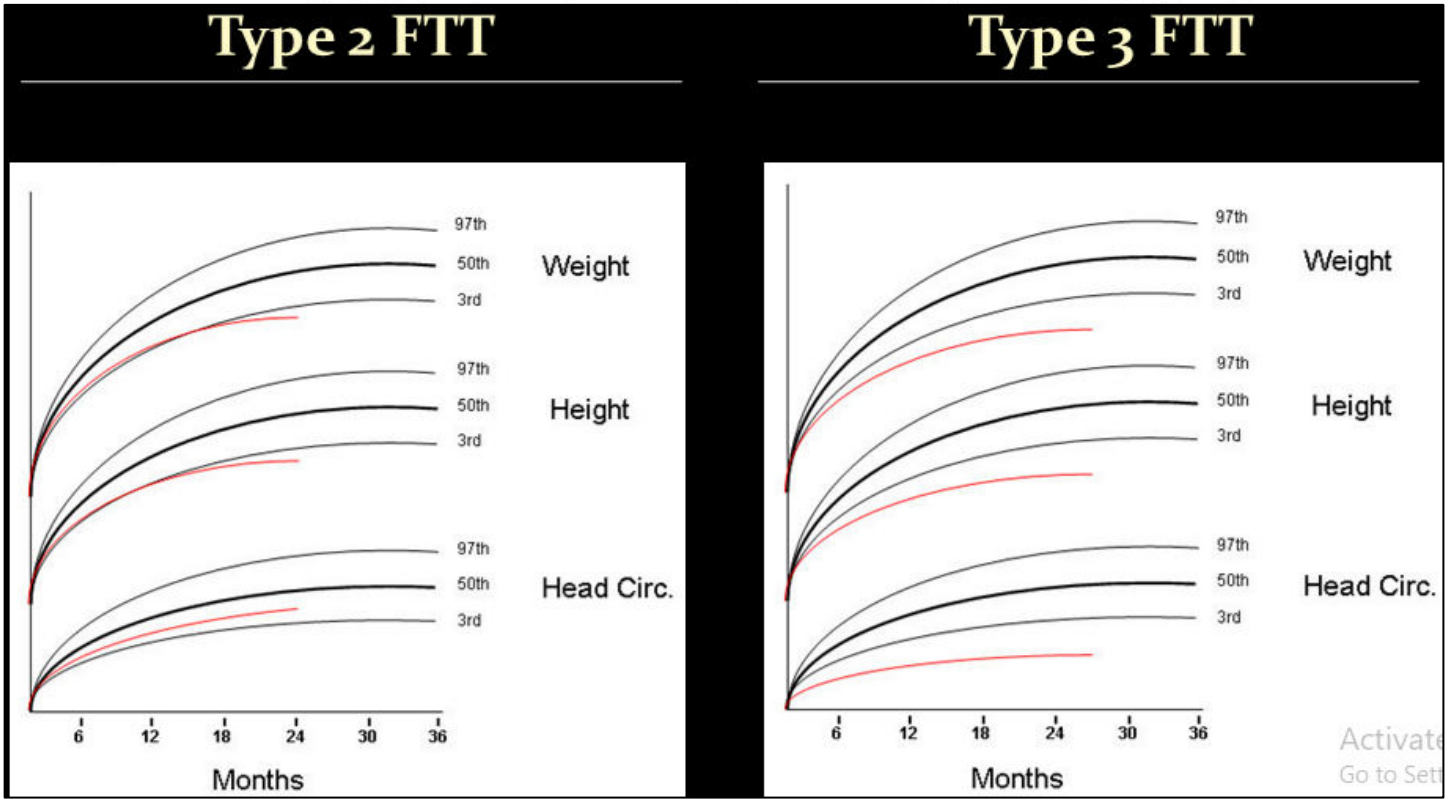


- ✓ Gender: Female
- ✓ Age = 4-year-old
- ✓ Height: 80 Cm



- ✓ Gender: Male
- ✓ Age: 11-year-old
- ✓ Height: 120 cm

Short stature & FTT:



Classification of short stature :

<u>Cause:</u>

- Physiologic ss.
- Pathologic ss.

<u>US:LS ratio</u>

- Proportionate SS.

- Disproportionate SS.
  Short limbs & Short trunk.

Proportionate SS.

Normal variant :

. FSS.
. CDGP.

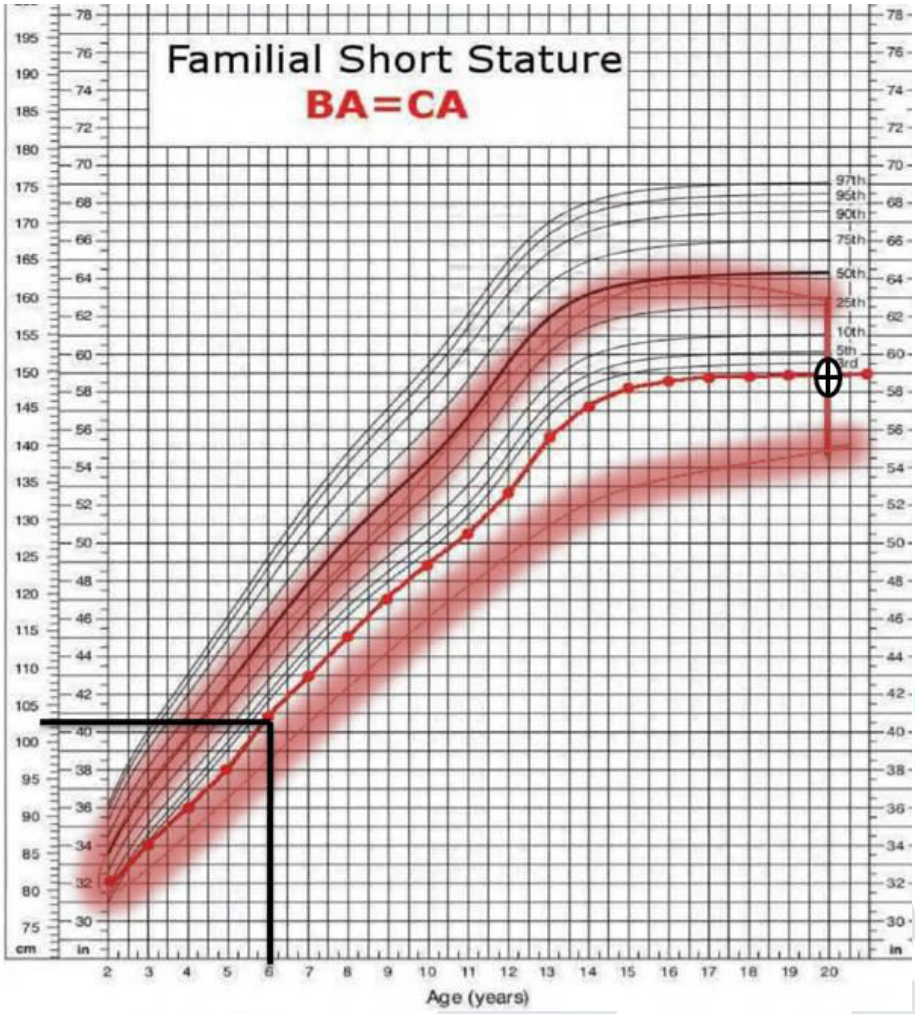
Prenatal causes:

. IUGR.
. Prenatal infection (TORCH).
. Genetic syndromes (Down's, Turner, Seckle, prader-willi & Noonan syndromes).

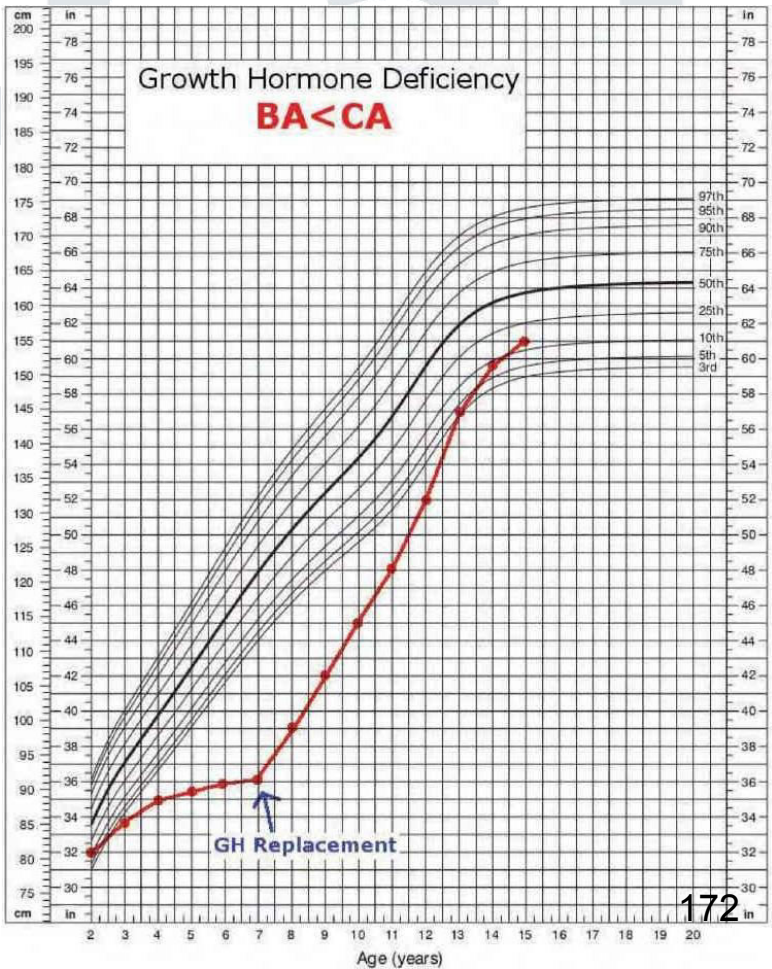
Systemic causes:

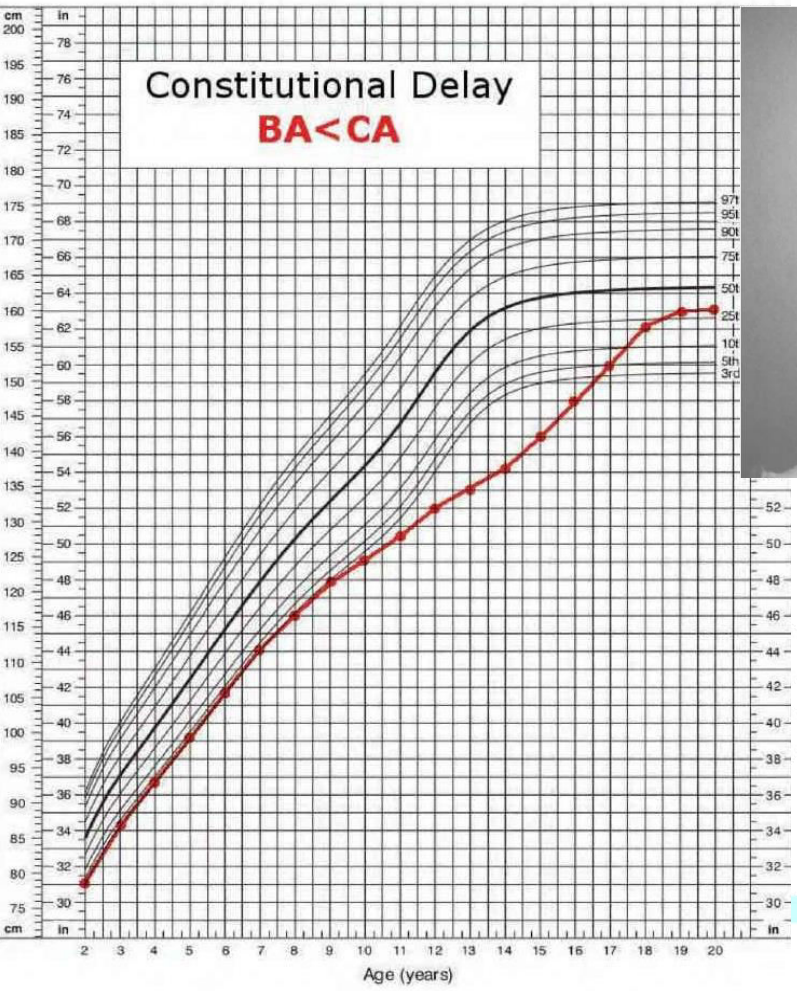
. Sever long standing malnutrition.
. Chronic disease (eg; CKD).
. Malabsorption (eg; Celiac disease).
. Endocrine (eg; GH deficiency & Cushing's syndrome).
. Psychosocial deprivation.

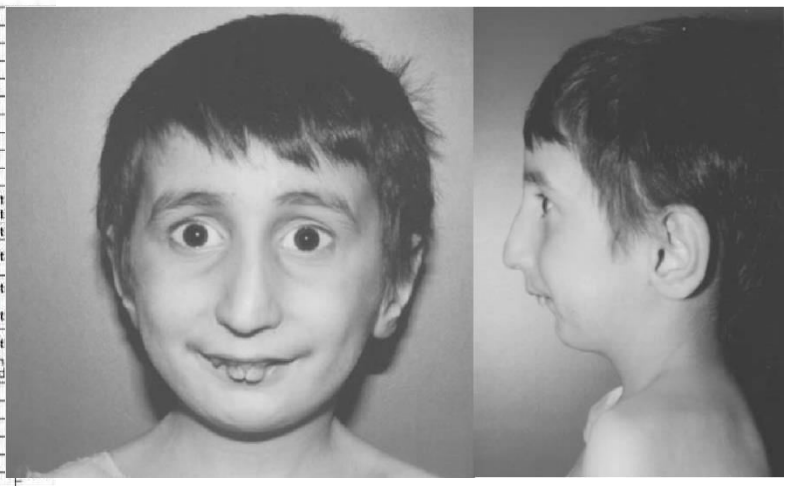
FSS	CDGP
Child's height is less than 3rd percentile of expected according to age and gender but it is normal for his target height (mid parental height).	Child's height is less than expected during childhood, but the final adult height is normal.
Normal puberty.	Delayed puberty.
Family history of short stature.	Family history of delayed puberty.
Bone age = Chronological age.	Bone < chronological age.

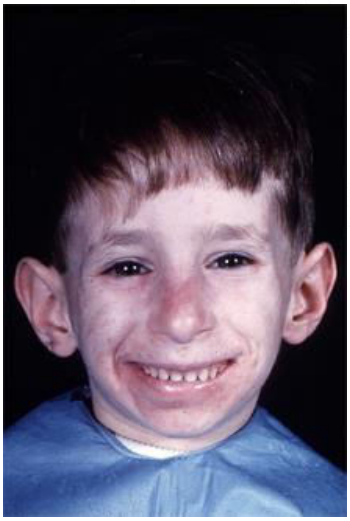

Familial Short Stature
BA=CA
97th
95th
90th
75th
50th
25th
10th
5th
3rd
cm
in
Age (years)

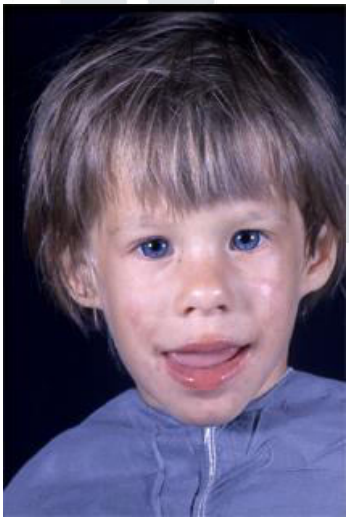
MPH = 150 cm

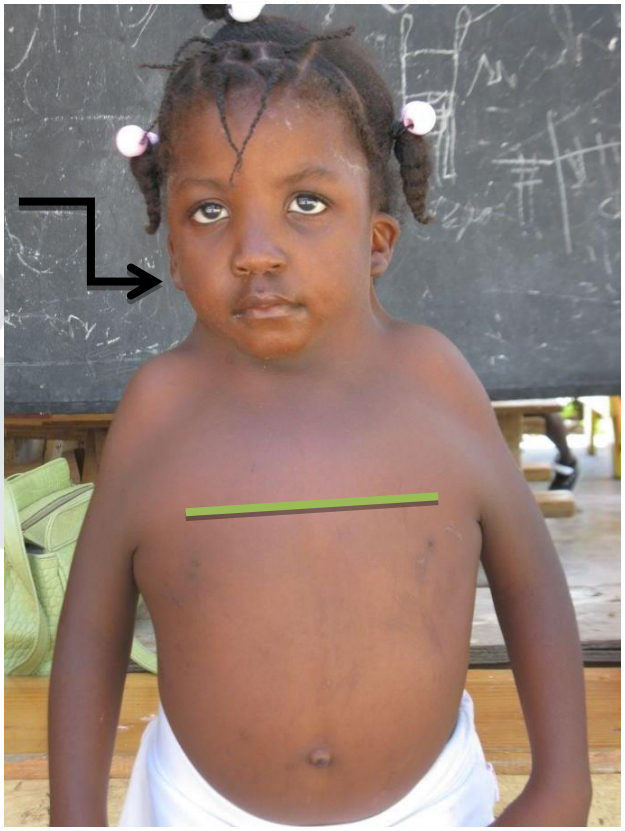

Growth Hormone Deficiency
BA<CA
97th
95th
90th
75th
50th
25th
10th
5th
3rd
GH Replacement
cm
in
Age (years)







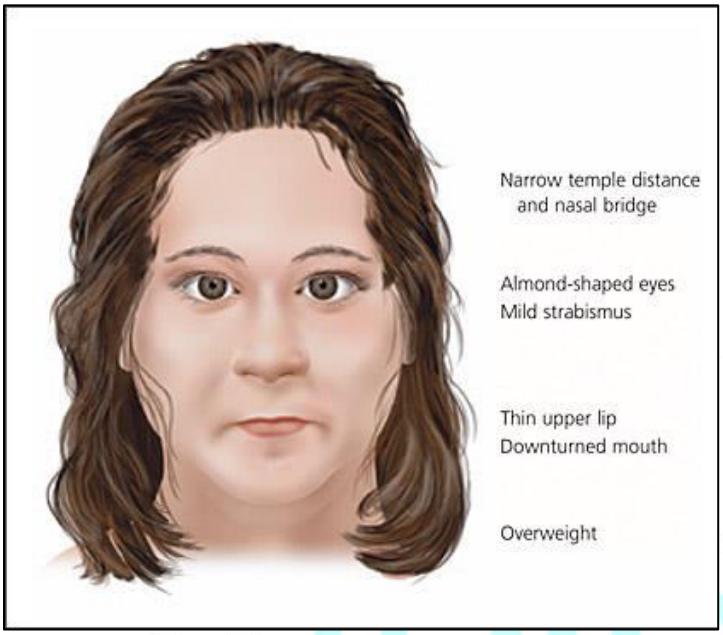


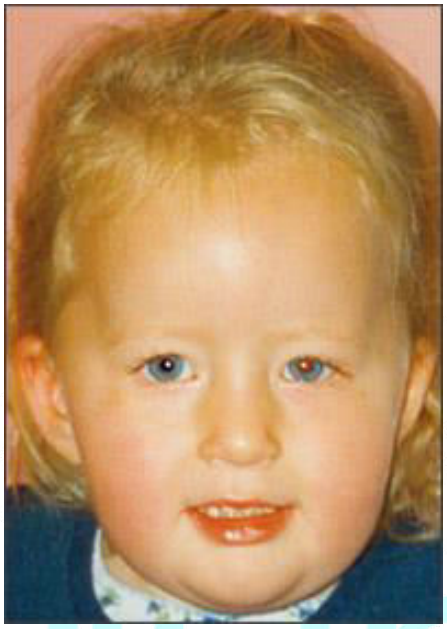


Turner syndrome

- Turner syndrome is an important consideration in girls with short stature and especially growth failure, because shortness may be the presenting feature of the syndrome.
- Virtually all girls with Turner syndrome have short stature, with an average adult height about 20 cm shorter than predicted by the mid-parental height.

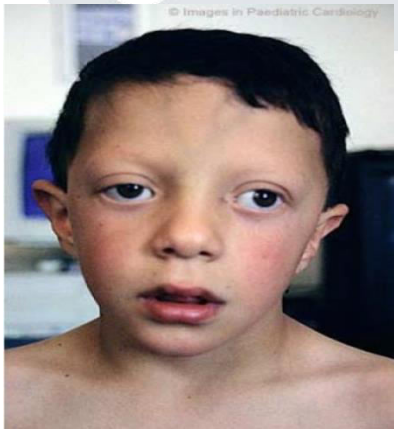
- In addition, affected patients usually have absent or very delayed pubertal development and may have a square "shield" chest, webbed neck, cubitus valgus (increased carrying angle of the arm), genu valgum (inward tilting knees), shortened fourth metacarpals, and Madelung deformity of the forearm .
- Prompt diagnosis of Turner Syndrome is important because of associated cardiovascular, renal, and endocrine abnormalities, which may require treatment, including growth hormone therapy.

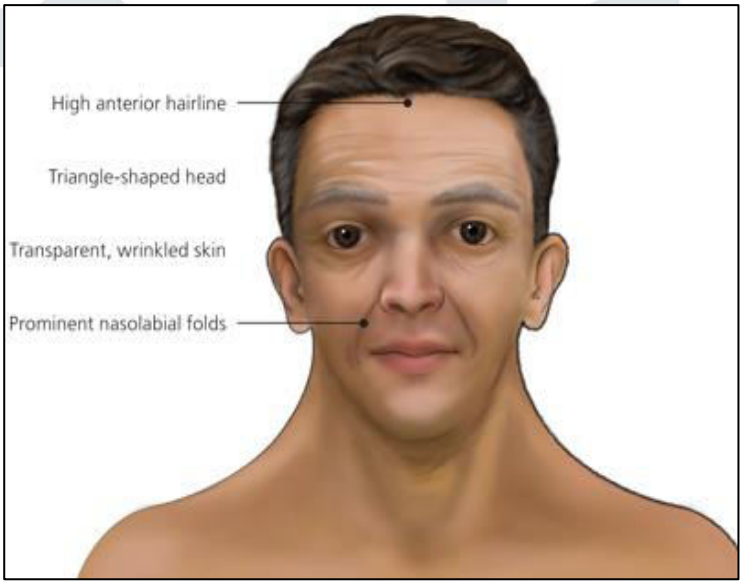




Prader-Willi syndrome

- Prader-Willi syndrome (PWS) is the most common syndromic form of obesity. Obesity and hyperphagia typically develop during early childhood and can be severe. Other common clinical characteristics are hypotonia and feeding problems during infancy, developmental delay, and hypogonadism.
- Short stature is common but may not develop until late childhood when the child fails to undergo a pubertal growth spurt.
- Treatment with growth hormone improves linear growth and body composition.





Noonan syndrome

- Noonan syndrome is a relatively common autosomal dominant disorder that is associated with short stature and congenital heart disease (CHD), most often pulmonic stenosis. It is clinically and genetically heterogeneous.
- The most consistent clinical features are widely spaced eyes and low-set ears (>80 percent), short stature (>70 percent), and pulmonic stenosis (approximately 50 percent) .

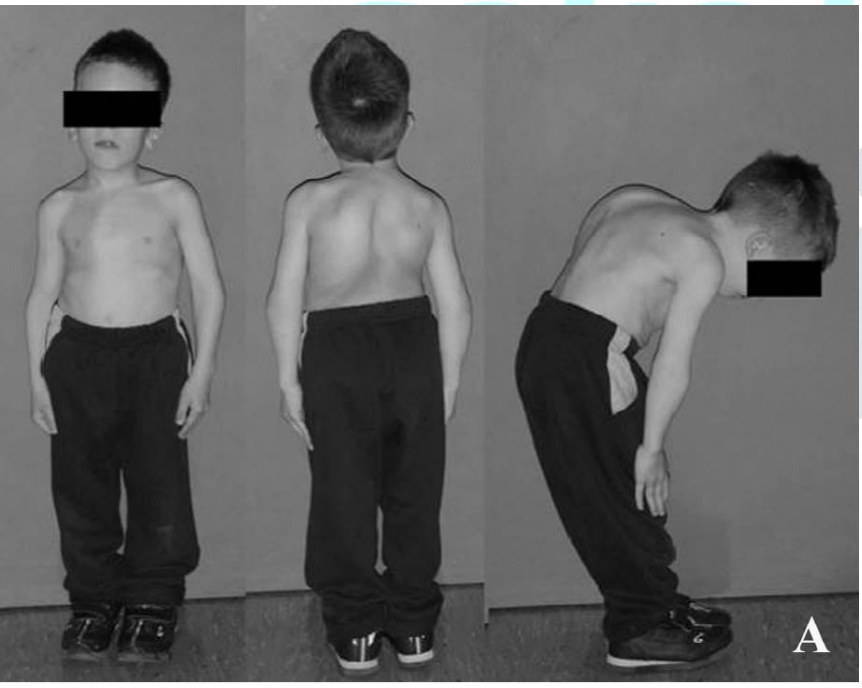
Disproportionate SS.:

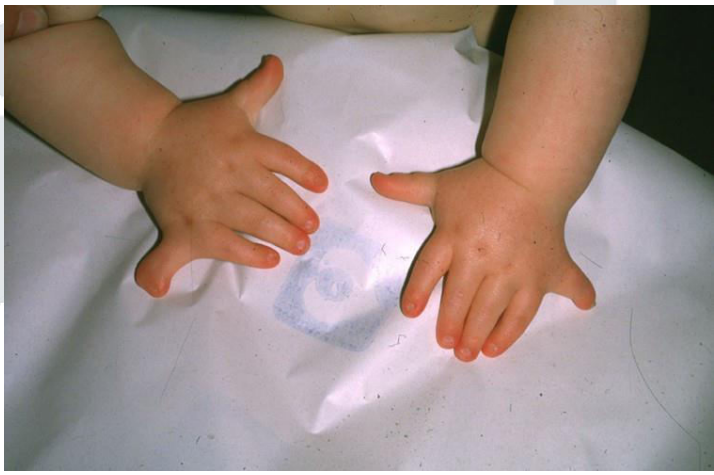
Short trunk dwarfism (low US:LS)

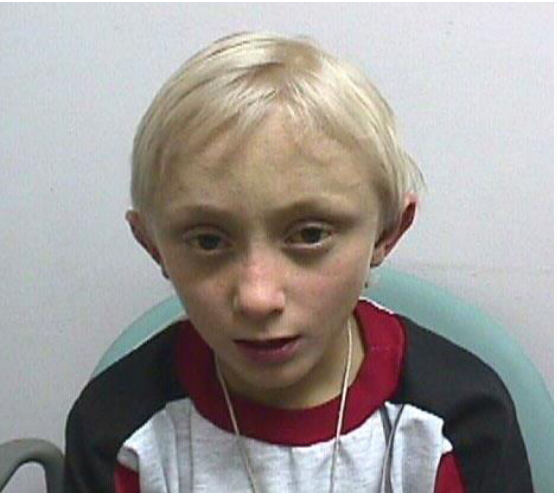
- Spondyloepiphyseal dysplasia.
- Mucopolysaccharidosis.
- Mucolipdosis.
- Pott's disease.
- Hemivertebra\ butterfly vertebra.

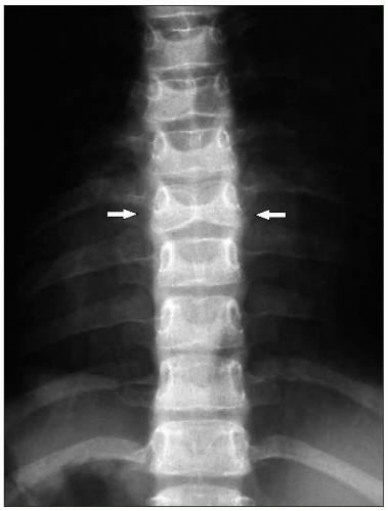
Short limb dwarfism (High US:LS)

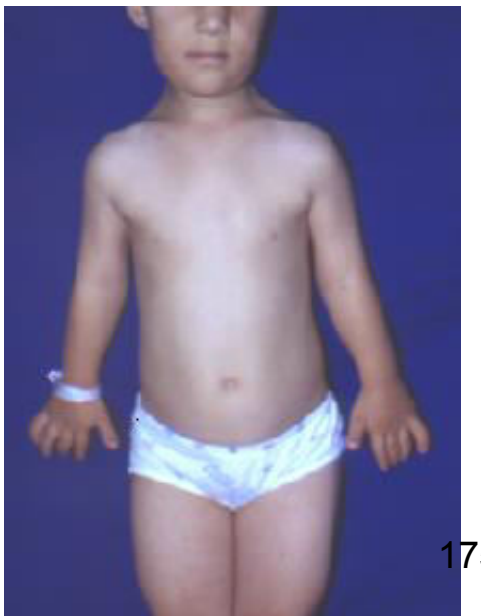
- Rickets.
- Achondroplasia.
- Osteogenesis imperfecta.
- Congenital hypothyroidism.
- Chondroectodermal dysplasia.

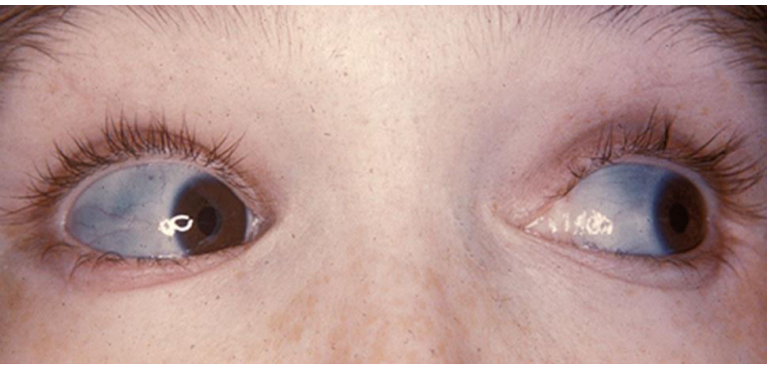








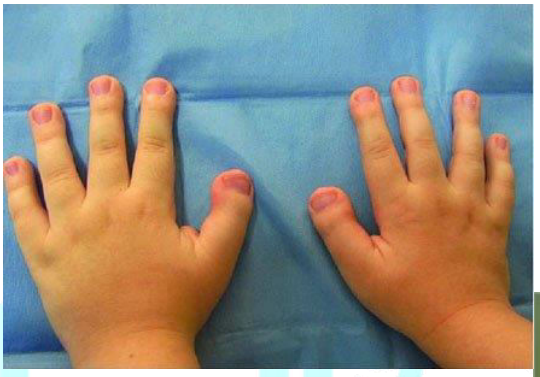


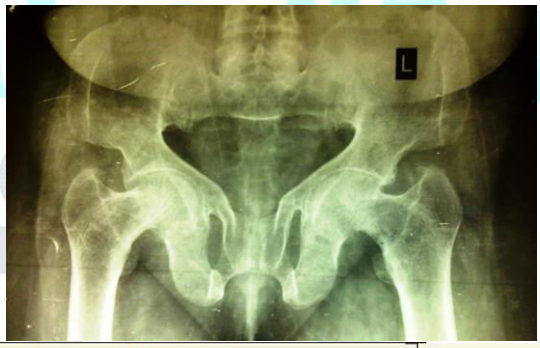


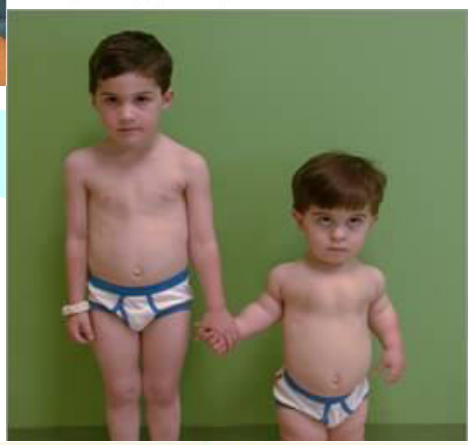
Achondroplasia

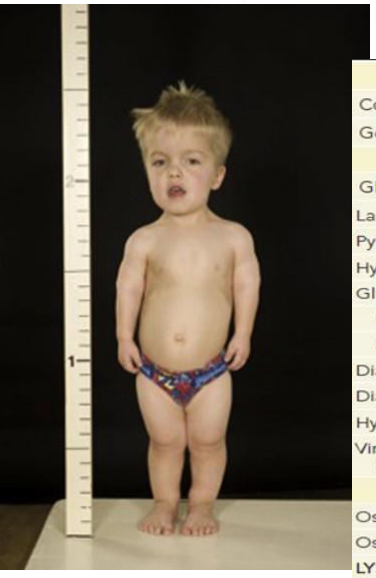
- Autosomal dominant inheritance, Mutation in FGFR3.
- Champagne glass pelvis.
- Hand abnormality.
- Obesity.
- Neurologic problems.

- Delayed motor milestones.
- Recognized at birth.
- Bowing of legs.
- Proximal limb shortening.









VARIATIONS OF NORMAL
Constitutional (delayed bone age)
Genetic (short familial height)
ENDOCRINE DISORDERS
GH deficiency
Laron dwarfism (increased GH and decreased IGF-1)
Pygmies (normal GH and IGF-2 but decreased IGF-1)
Hypothyroidism
Glucocorticoid excess
Endogenous
Exogenous
Diabetes mellitus under poor control
Diabetes insipidus (untreated)
Hypophosphatemic vitamin D-resistant rickets
Virilizing congenital adrenal hyperplasia (tall child, short adult) $P\text{-}450_{c21}$, $P\text{-}450_{c11}$ deficiencies
SKELETAL DYSPLASIAS
Osteogenesis imperfecta
Osteochondrodysplasias
LYSOSOMAL STORAGE DISEASES
Mucopolysaccharidoses
Mucolipidoses

SYNDROMES OF SHORT STATURE
Turner syndrome (syndrome of gonadal dysgenesis)
Noonan syndrome (pseudo-Turner syndrome)
Autosomal trisomy 13, 18, 21
Laurence-Moon-Bardet-Biedl syndrome
Prader-Willi syndrome
Autosomal abnormalities
Dysmorphic syndromes (e.g., Russell-Silver or Cornelia de Lange syndrome)
Pseudohypoparathyroidism

CHRONIC DISEASE
Cardiac disorders
Left-to-right shunt
Heart failure
Pulmonary disorders
Cystic fibrosis
Asthma (severe steroid dependent)
Gastrointestinal disorders
Malabsorption (e.g., celiac disease)
Disorders of swallowing
Inflammatory bowel disease
Hepatic disorders
Hematologic disorders
Sickle cell anemia
Thalassemia
Renal disorders
Renal tubular acidosis
Chronic uremia
Immunologic disorders
Connective tissue disease
Juvenile idiopathic arthritis
Chronic infection
AIDS
Hereditary fructose intolerance
Malnutrition
Kwashiorkor, marasmus
Iron deficiency
Zinc deficiency
Anorexia caused by chemotherapy for neoplasms
Cerebral palsy

HOW TO APPROACH?

Approach to a child with short stature

1. History
2. Anthropometric measurements
3. Plotting on growth chart
4. Physical examination
5. workup

History

- Birth history
- Nutritional history
- Family history
- Drugs (steroids)
- Chronic diseases

Perinatal:

. Infections, placental insufficiency, poor nutrition, and medication side effect can impair fetal growth and development.
. Birth measurements reflect intrauterine conditions.
. may point to specific pathologies (hypopituitarism,hypothyroidism)

Nutritional:

. Malnutrition is the most common cause of poor growth worldwide;a detailed history of quality and quantity of nutrition is needed in the evaluation of abnormal growth
. a 24-hour food recall or three-day food diary for evaluation.
. Ask about nutrition (problems with feeding, appetite, special diets or any other indication of inadequate nutrition)

Family

. Father's height and age during pubertal growth spurt
. mother's height and age at menarche
. heights of siblings
. medical conditions of family members.
. The heights of parents determine the heights of their children; most children also follow their parents

History of chronic diseases

through system review to exclude chronic infections and chronic illnesses.

- GIT : Chronic diarrhea, abdominal pain and GIT bleeding→ IBD.
  Diarrhea, weight loss and abdominal distention → Coeliac disease
- Respiratory: Recurrent adenoid → CF / Long history of uncontrolled asthma
- Renal: Polyuria and edema → CRF. / Polyuria, rickets → RTA./ Recurrent UTI → CRF.

- Others: Poor academic performance →Hypothyroidism.
  Recurrent infections and poor wound healing → Immunodeficiency.

Clues to etiology from history

History	Etiology
History of delay of puberty in parents	Constitutional delay of growth
Low Birth Weight	Small GA
Neonatal hypoglycemia, jaundice, micropenis	GH deficiency
Dietary intake	Under nutrition
Headache, vomiting, visual problem	Pituitary/ hypothalamic Space occuping lesions
Lethargy, constipation, weight gain	Hypothyroidism
Polyuria	CRF, RTA
Social history	Psychosocial dwarfism
Diarrhea, greasy stools	Malabsorption

Anthropometric measurements

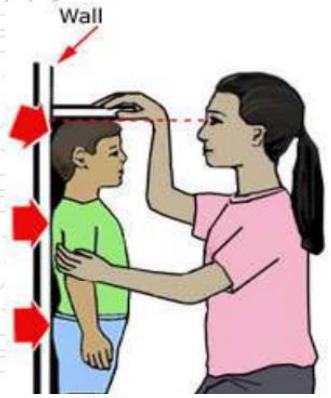
- Height measurements:

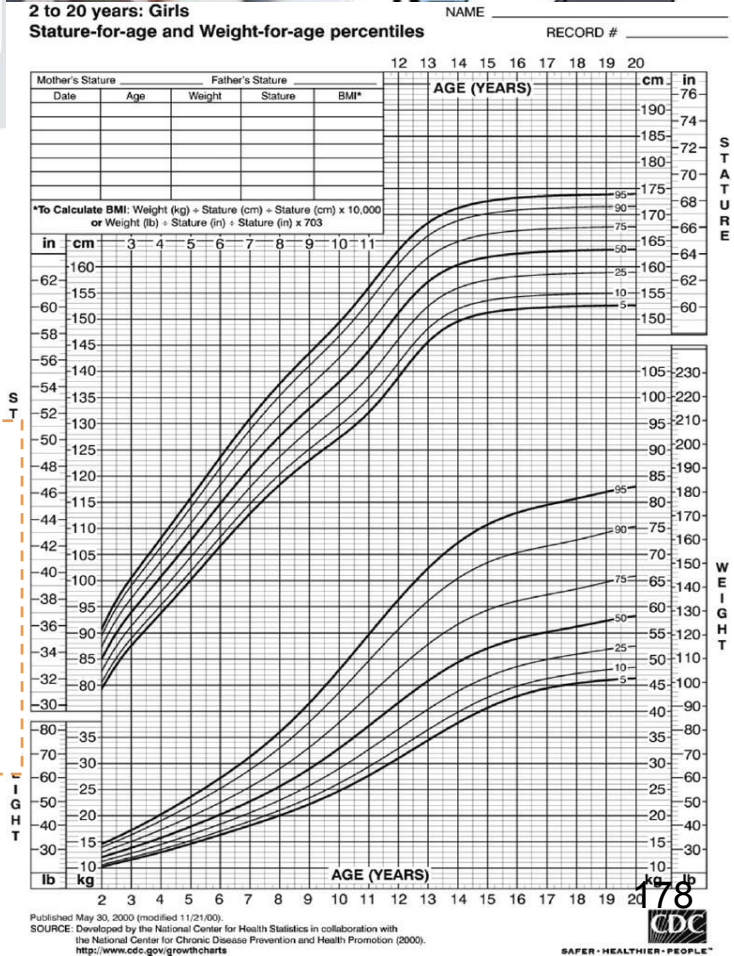
. Without footwear
. Heels & back touching the wall
. Looking straight ahead

- Also we calculate the midparental hight in children

<u>Accurate height measurement:</u>

. Below 2 yrs supine length with infantometer
. For older children Harpenden Stadiometer





-Normal birth length 50cm

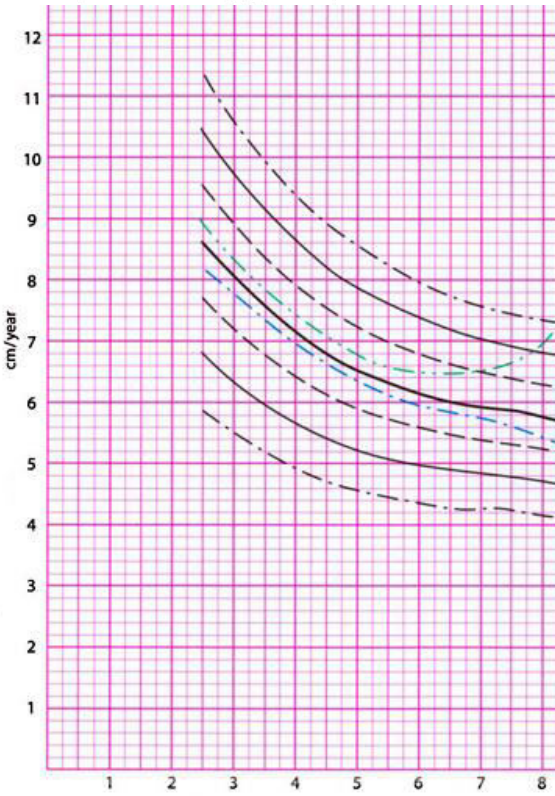
-Expected growth

. 1st year 25cm
. 2nd year 12cm
. 3rd year onwards 6-10cm per year until puberty

Growth Velocity

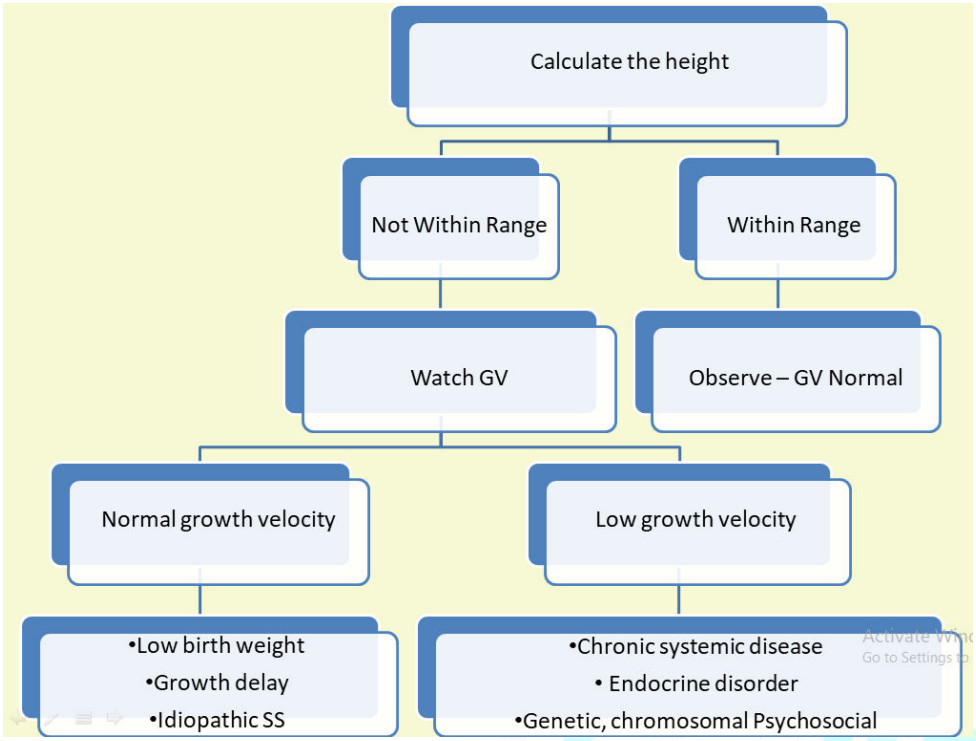
- The change in growth over time and its the most critical factor in evaluating the growth.
- Calculate growth velocity as the change in standing height over at least 6 months (in children) or in length over at least 4 months (in infants)
- Observation of child's height pattern in the form of “CROSSING PERCENTILE LINES” on a linear growth curve is the simplest
- method of observing abnormal growth velocity.

- $Growth\ velocity = \frac{Height\ (cm) at\ time2 - Height (cm) at\ time1}{Time2 - Time1 (months)} \times 12 (months/year)$



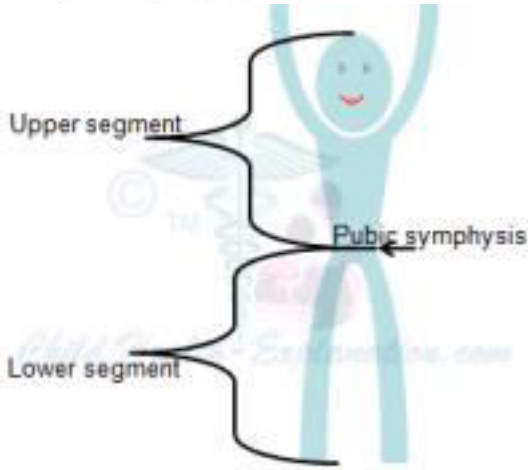
Normal Growth Velocity by Age:

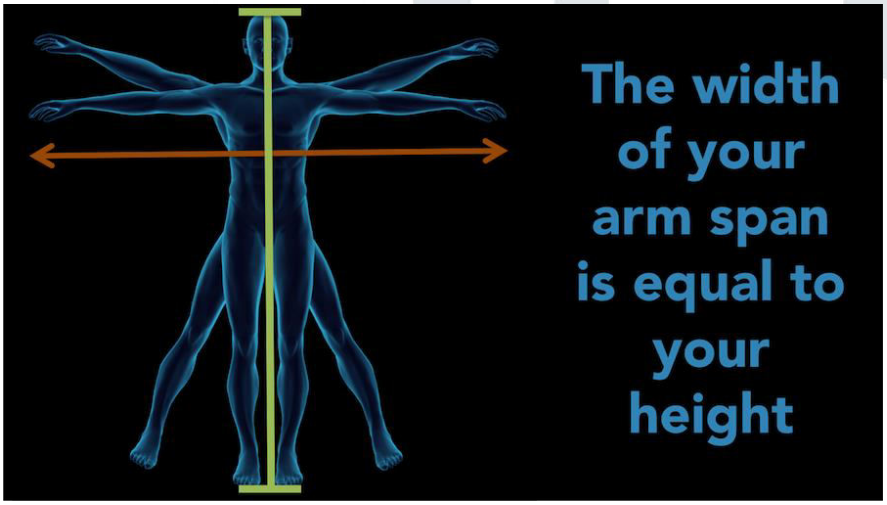
AGE	GROWTH VELOCITY PER YEAR
Birth to 12 months	23 to 27 cm
12 months to 1 year	10 to 14 cm
2 to 3 years	8 cm
3 to 5 years	7 cm
5 years to puberty	5 to 6 cm
Puberty	Girls: 8 to 12 cm
	Boys: 10 to 14 cm

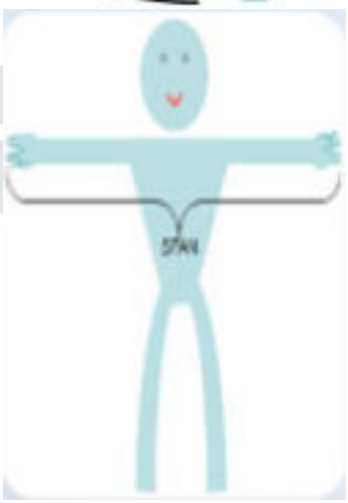


Assessment of body proportion

- Lower segment (LS) pubic symphysis to ground
- Upper segment (US) total height/length – LS
- US to LS ratio is 1.7 at birth decreases by 0.1 every year to reach 1 at 7 to 10 years of age.
- Arm span

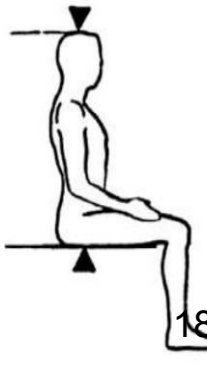






How to measure upper and lower segments?

You should measure the upper segment (US) then by using the total height you will obtain LS. Upper segment is the sitting height.



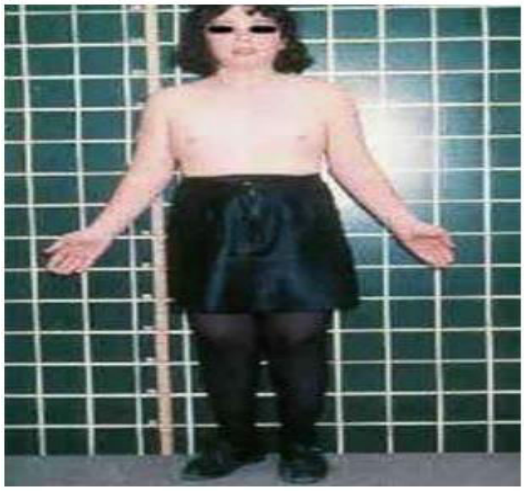
Upper segment : Lower segment ratio

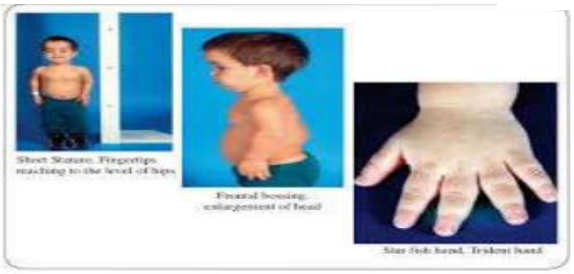
-*Increase:* Achondroplasia, Skeletal dyspalsias, untreated hypothyroidism

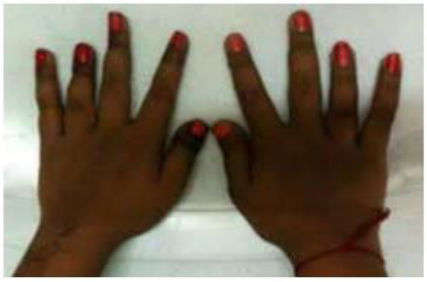
-*Decrease*: Short trunk (scoliosis), Short neck (klippel-Feil syndrome), Arachnodactyly (Marfan's homocystinuria)

hands and feet examination:

- Short 4 th metacarpal → Turner.
- Trident hand → achondroplasia.
- Wide carrying angle → Turner.
- Asymmetry → Russell silver syndrome.

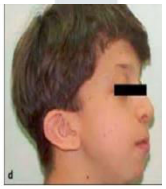


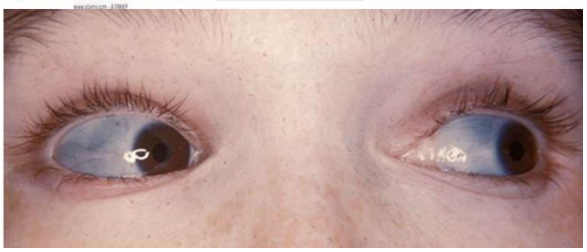




head and neck

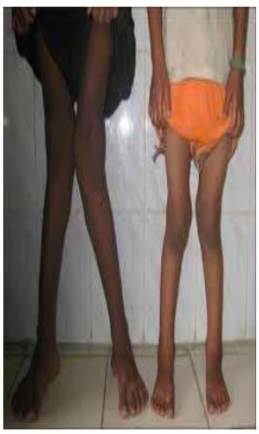
- Short webbed neck → Turner and Noonan.
- Low posterior hair line → Turner.
- Low set ears → Noonan.
- Coarse features → Mucopolysaccharidosis.
- Blue sclera → osteogenesis imperfecta.





lower limbs

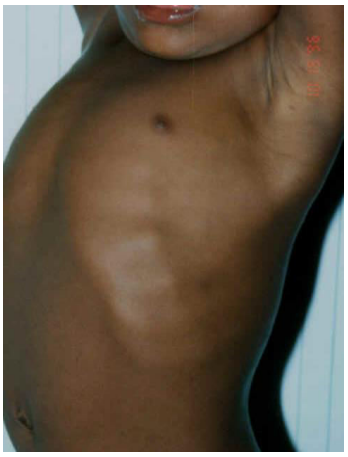
- Bow legs and other signs of rickets



chest and abdomen

- Rosary beads → Rickets.
- Wide spaced nipple →Turner
- Distended abdomen → Coeliac.

- Hepatosplenomegaly →thalassemia.
- Stria→Cushing syndrome.



Clues to etiology from examination

Examination finding
Disproportion
Dimorphism
Pallor
Hypertension
Frontal bossing, depressed nasal bridg crowed teeth, small penis
Goiter, coarse skin
Central obesity, striae

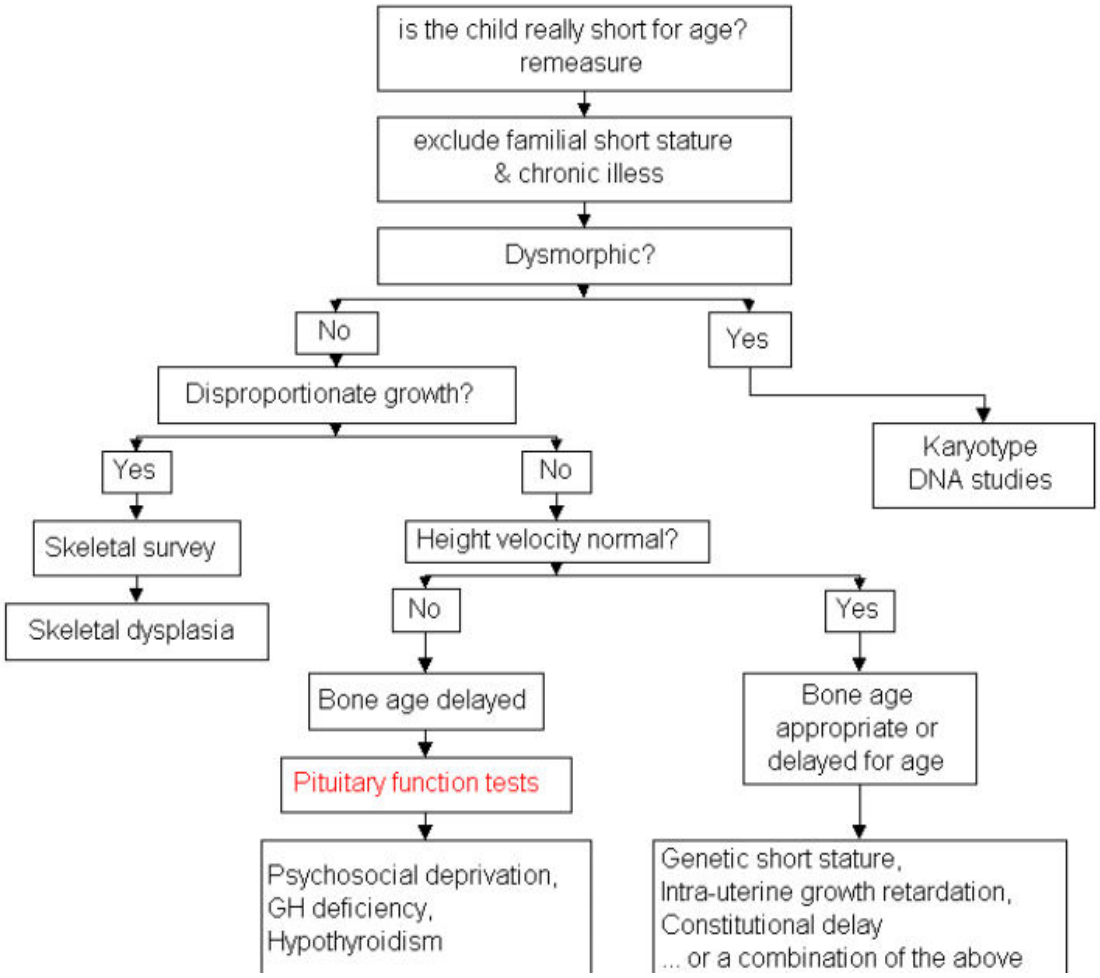


Table 173-4	Growth Failure: Screening Tests
TEST	**RATIONALE**
CBC	*Anemia:* nutritional, chronic disease, malignancy
	Leukopenia: bone marrow failure syndromes
	Thrombocytopenia: malignancy, infection
ESR, CRP	Inflammation of infection, inflammatory diseases, malignancy
Metabolic panel (electrolytes, liver enzymes, BUN)	Signs of acute or chronic hepatic, renal, adrenal dysfunction; hydration and acid-base status
Carotene, folate, and prothrombin time; celiac antibody panel	Assess malabsorption; detect celiac disease
Urinalysis with pH	Signs of renal dysfunction, hydration, water and salt homeostasis; renal tubular acidosis
Karyotype	Determines Turner (XO) or other syndromes
Cranial imaging (MRI)	Assesses hypothalamic-pituitary tumors (craniopharyngioma, glioma, germinoma) or congenital midline defects
Bone age	Compare with height age and evaluate height potential
IGF-1, IGF-BP3	Reflects growth hormone status or nutrition
Free thyroxine	Detects panhypopituitarism or isolated hypothyroidism
Prolactin	Elevated in hypothalamic dysfunction or destruction, suppressed in pituitary disease

bone age:

Perform anteroposterior radiography of left hand and wrist to assess bone age.

BA = bone age.
CA = chronological age

	CA > BA	CA = BA	CA < BA
Normal growth velocity	Constitutional delay of growth	Familial short stature	———
Abnormal growth velocity	Malnutrition, chronic systemic disorders or endocrine disorders	Malnutrition or chromosomal disorder	Precocious puberty

GH deficiency:

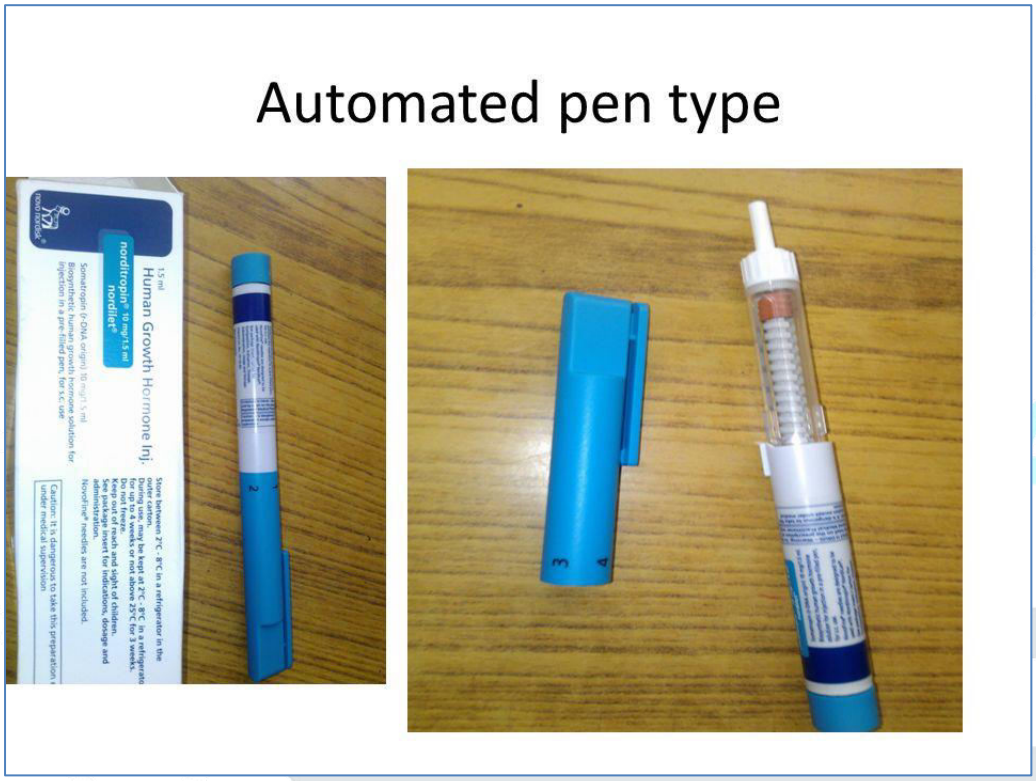
Evaluation of Suspected Growth Hormone Deficiency

History	• Birth weight and length • Obstetric complications • Neonatal hypoglycemia • Prolonged neonatal jaundice/giant cell hepatitis • Review of systems for systemic illness • Diet history
Physical exam	• Linear growth failure (may be the only clinical feature present) Proportionate short stature Low height velocity • Weight for length appropriate or increased • Micropenis in males • Small midface • High-pitched voice • Delayed dental eruption
Imaging	• Radiologic evaluation of bone age • Central nervous system imaging to evaluate the hypothalamus/pituitary and to exclude other conditions
Laboratory evaluation	• Measurements of IGF-1 and IGF-binding protein levels • Assess thyroid function • Exclude chronic medical illness CBC, metabolic profile, inflammatory markers, celiac testing, urinalysis • Determination of peak GH levels after stimulation test
Treatment Considerations	• Replacement with rhGH • Dosage adjustment IGF-1 Height velocity Pubertal status Body weight • Predictors of improved response to treatment Early initiation of treatment Higher rhGH dose
	• Monitor during treatment Height velocity IGF-1 levels Glucose metabolism Skeletal age Thyroid function, adrenal function

growth hormone therapy:

Indications :

- GHD
- Turner syndrome
- chronic renal failur
- Prader-Willi syndrome
- children born small for gestational age who have not reached 5 th centile by 2yrs.
- the long-term treatment of idiopathic short stature with height 2.25 SDs or less below the mean.



FOLLOW UP:

-required as treatment with GH carries the risk of an increased incidence of slipped capital femoral epiphysis, especially in rapidly growing adolescents, and of pseudotumor cerebri.

Flaccid paralysis

Poliomyelitis, Guillain-Barré Syndrome & Transverse Myelitis

Poliomyelitis:

Polioviruses

- Non-enveloped RNA-positive
- Belonges to Picornaviridae family, Enterovirus genus
- 3 antigenically distinct serotypes (1,2 & 3)
- Spreads from GIT to the CNS (Enteroviruses)feco-oral root
- Can retain activity at room temp. for days and can be stored frozen at -20˚C indefinitely
- Easily inactivated by heat (>56˚C), formaldehyde, chlorination and UV light

Epidemiology

- In 1952 about 58,000 cases were reported in the US (including ~21,000 cases of paralytic polio) that resulted in 3,000 deaths
- The epidemics mostly affected adolescents and young adults
- The universal use of Sabin and Salk vaccines has resulted in almost complete global eradication
- The most devastating outcome is paralysis
- 90% of infections are asymptomatic or inapparent (but do induce immunity)
- Clinically apparent but non-paralytic illness occurs in ~5% of all infections
- Paralytic polio occurs in:
  - 1/1,000 among infants (in developing countries)
  - 1/100 among adolescents (in developed countries before vaccinations)

Transmission

- Feco-oral route
- Humans are the only reservoir
- Virus has been isolated from stools more than 2 weeks before paralysis and several weeks after onset of symptoms

Pathogenesis

- Entry through GI
- 1^{ry} site of replication : M cells in small intestine
- Spread to regional LN
- 1^{ry} viremia after 2-3 days
- Seeding to different sites (RES, Sk.m., brown fat)
- 2^{ry} viremia occurs due to replication and release from RES
- CNS affected may be through (theories) :
  - Seeding due to 1^{ry} viremia
  - Access through peripheral nerves
- Exact mechanism is unknown
- **Virus never cultured from CSF of paralytic polio pts.**

- **Pts. With aseptic meningitis (due to polio) never had paralytic disease**
- Once access is gained, the virus may traverse through neuronal pathways and multiple sites within the CNS are affected
- **Mixed inflammatory reaction** (PMN and lymphocytes) results in extensive destruction, with petechial h'ges and local edema

  Tendency to affect motor neurons

- Most common sites of infection in CNS :
  - AHC
  - Medulla oblongata (CN nuclei : bublar polio)
- Less commonly :
  - Reticular formation & Brain stem (a/w bulbar polio)
  - Intermediate and dorsal horncells and dorsal root ganglia

Immunity:

- Infants acquire immunity trans-placentally
- Immunity wanes at variable rates during first 4-6 mo. of life
- **Active immunity after natural disease is lifelong but is only against the infecting serotype**
- Polio neutralizing Ab develop several days after exposure
- IgG protects against CNS invasion !!?
- IgA protects against re-infection through GI

Clinical Manifestaion:

- I.P. 8-12 days
- Infection follows on of several courses
  - In-apparent infection (~90%,)
  - Abortive polio
  - Non-paralytic polio
  - Paralytic polio
- Paralysis (if occurs) appears 3-8 days after initial symptoms

Abortive Poliomyelitis

- ~5% of cases
- Non-specific flu-like symptoms
- Occurs 1-2 wks after infection
- Fever, malaise, anorexia and headache
- May have sore throat, abd. Pain, myalgias
- Short-lived (2-3 days)
- P/E normal or insignificant
- Recovery is complete with no sequel

Non-paralytic Polio

- ~1% of cases
- Signs of abortive polio but headache , nausea , vomiting are more intense
- Sore and stiff posterior muscles of neck and trunk
- Symptom-free period occurs between minor and major illness (CNS)
- Nuchal and spinal rigidity are the basic for diagnosis of second phase non-paralytic polio
- P/E reveals
  - nuchal and spinal rigidity
  - Changes in superficial and/or deep reflexes
  - If open anterior fontanel may be tense or bulging

How to examine nuchal/spinal rigidity

- Meningeal signs (kernig's, brudzinski's, passive neck flexion)
- From supine-sitting (w/o support)
- When supine touch the chest with your chin
- When supine, hold the knees, ask to sit
- Head drop

Reflexes

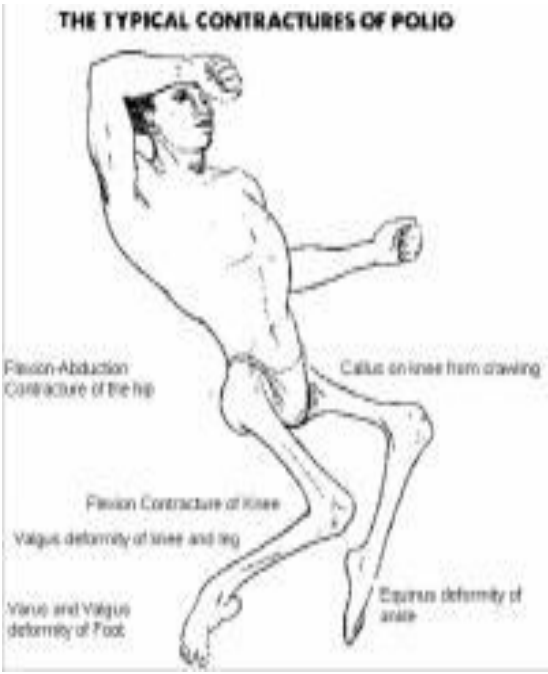
- Changes in reflexes whether inc. or dec. may precede weakness by 12-24 hrs
- Superficial reflexes (abdominal, cremastric …) are first to diminish
- Changes in deep tendon reflexes occurs 8-24 hrs after superficial reflexes are diminished and indicate impending paresis

Paralytic Polio

- 0.1% of persons infected
- 3 clinically recognized syndromes, according to site of involvement :
  - Spinal Paralytic Polio
  - Bulbar Paralytic Polio
  - Polio-encephalitis

Spinal Paralytic Polio (SPP)

- Occurs as the second phase of a biphasic illness (the 1st resembles abortive polio)
- b/w the phases there are no symptoms and the pt. feels better for about 2-5 days
- After which severe headache and fever appear with exacerbation of the previous symptoms
- Severe muscle pain and sensory and motor phenomena (paraesthesias, hypersthesias, fasiculations and spasms)
- O/E the distribution of paralysis is spotty (single or multiple muscles, or group of muscles may be affected by any pattern)
- Within 1-2 days, asymmetric flaccid paralysis or paresis occurs
- Involvement of one leg is common followed by one arm



- Proximal muscles are affected more than distal ones
- Nuchal/spinal stiffness, muscle tenderness
- Hyperreflexia followed by hypo/areflexia
- Sensation is intact (if not re-consider the diagnosis)
- The paralytic phase is extremely variable
- Some, progress from paresis to paralysis
- Some, recover (either slowly or rapidly)
- Progression of neurological manifestation is rare after 2-3 days of onset
- Paralysis of the lower limb is often a/w bowel and bladder dysfunction ranging from transient incontinence to paralysis with constipation and urinary retention
- Little recovery from paralysis is noted in the first days, but if any, will be evident mostly after 6mo.
- The return of strength and reflexes is slow and may continue over 18mo.
- Lack of improvement over the first few weeks may predict permanent paralysis
- When it occurs, atrophy failure of growth and deformity may develop

Bulbar Poliomyelitis

- Dysfunction of cranial nerves and/or medullary centers
- Clinical findings are extensive :
  - Nasal twang of voice and crying (consonants)
  - Inability to swallow smoothly, accum. Of secretion and interfere with respiration rhythm
  - Absent or ineffective cough reflexes
  - Nasal regurgitation
  - Deviation of the palate, uvula or tongue
  - Paralysis of vocal cord/s (hoarseness, aphonia or asphyxia)
  - ROPE sign (retracted hyoid bone)

- Involvement of vital centers :
  - Irregularities in rate, depth and rhythm of resp
  - Cardiovascular alteration (mainly inc. BP, arrhythmia)
  - Flushing and mottling of skin
  - Rapid changes in body temp.
- Uncommon presentation is ascending paralysis (Landry type)
- Course of bulbar polio is variable and rarely permenant

Polio-encephalitis

- Rare form
- Higher centers of the brain are involved
- Same manifestation of other viral encephalitis
- Seizures, coma, spastic paralysis with exaggerated reflexes (UMNL)
- Irritability, disorientation and tremors -Respiratory insufficiency

Paralytic polio with Ventilatory Insufficiency

- Higher vs. lower (respiratory muscle paralysis)
- In resp. m. paralysis :
  - Anxious expression
  - Short jerky breathless sentences
  - Inc. RR
  - Flaring and using of accessory muscles
  - Paradoxical abdominal movement during respiration (check deltoid)
  - Relative immobility of ICS (segm. Uni. Bil.)

Diagnosis

- Should be considered in any unimmunized or incompletely immunized child presenting with nonspecific febrile illness, aseptic meningitis or paralytic disease
- Vaccine associated polio (VAPP) is considered in any child with paralytic disease occurring 7-14 days after OPV

- WHO recommendation for Dx :
  - Isolation and identification of the virus in the stool with specific identification of wild vs. vaccine types (DNA sequence analysis)
  - 2 stool specimens collected 24-48 hrs apart
- Poliovirus concentration is highest during 1st week after onset of paralysis
- Constipation may be problematic
- CSF analysis :
  - Normal during minor illness
  - Pleocytosis (20-300cells/mm3) during CNS inv.
  - Cells may be PMN initially but shift to mononuclear later
  - By 2nd week of major illness CSF finding return back to near-normal
  - Protein may rise (50-100mg/dL) during this week
- Serological testing
  - Raised Ab titers fourfolds during acute phase to 3-6 wks later

Differential Diagnosis

- Guillain-Barré syndrome
- Transverse myelitis
- Traumatic paralysis (Sciatic nerve injury)

Management

- Mainly supportive
- Prevention of progression
- Prevent skeletal deformities
- Prepare parent for prolonged treatment
- <u>All IM inj. and surgical procedures are C/I during the acute phase of illness (may progress)</u>

Abortive Polio

- Supportive
  - Analgesics
  - Sedatives
  - Bed rest
  - Avoid exertion
- F/U 2mo. Later

Non-paralytic Polio

- Similar to abortive polio
  - Relief muscle discomfort and spasm
  - Hot packs
  - Hot baths
  - Firm bed
  - Gentle physical therapy
- F/U 2mo. Later

Paralytic Polio

- Requires Admission
- Suitable body alignment (neutral position, changed q3-6hrs)
- Opiates/sedatives unless C/I
- Manage constipation
- Manage urine retention (bethanechol)
- Consult orthopedist and psychiatrist
- Pure bulbar polio :
  - Maintain airway
  - Avoid risk of inhalation (head-low position)
  - BP closely monitored
  - Sometimes tracheostomy and MV are indicated

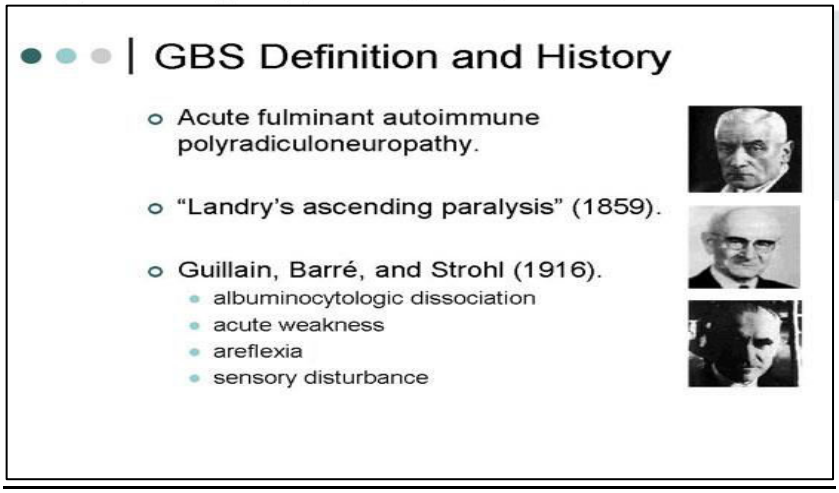
Complications

- Melena (may need transfusion)
- Acute gastric dilatation (decompression)
- HTN
- Hypercalcaemia, renal stones (immobility)
- UTI (stasis)
- Post-polio syndrome
  - 30-40yrs later
  - 30-40% of pts. Who survived paralytic polio
  - Severe myalgia
  - Exacerbation of existing weakness or even new weakness or paralysis

Prevention

- Vaccination is the only effective method
- Hygienic measures limit transmission among young children
- Inactivated polio vaccine (IPV)
- Oral polio vaccine (OPV)
- IPV induce immunity against the 3 strains
- OPV induce immunity against 2 strains
- IPV induces IgG
- OPV induces secretory IgA
- Immunogenicity of IPV is not affected by maternal Ab
- IPV has no adverse reactions
- OPV may cause VAPP in 1/6.2million (live attenuated)
- In the US only IPV is used (4 doses at 2m,4m,6m,4-6yrs)
- In Jordan four doses – 2m,3m,4m,9m
- In 1988, WHO set a strategy to eradicate polio by the year 2000
  - Routine immunization
  - National Immunization Days
  - Acute Flaccid paralysis surveillance
- OPV was used
- Vaccine-derived poliovirus (VDPV) which is stored in labs may acquire neurovirulent and transmission characteristic of the wild type
- This happened in Egypt 1993 and Philippines 2000

Guillain-Barré Syndrome (GBS)

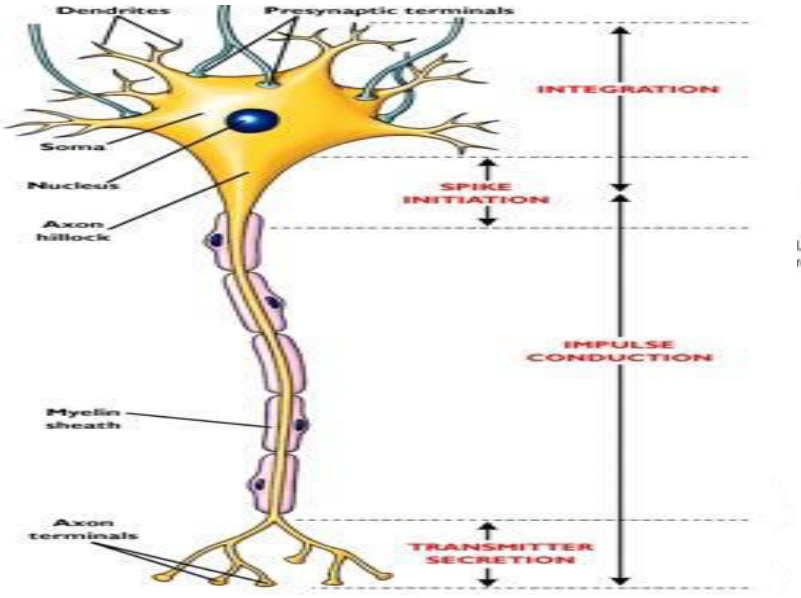


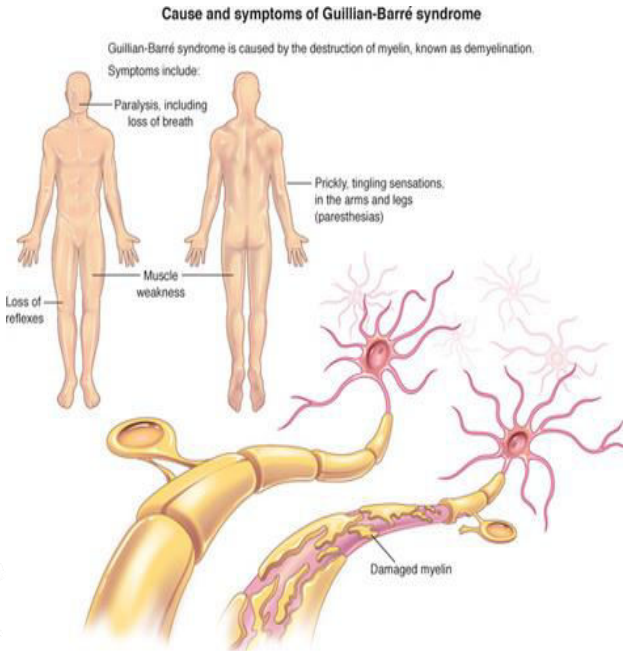
Introduction

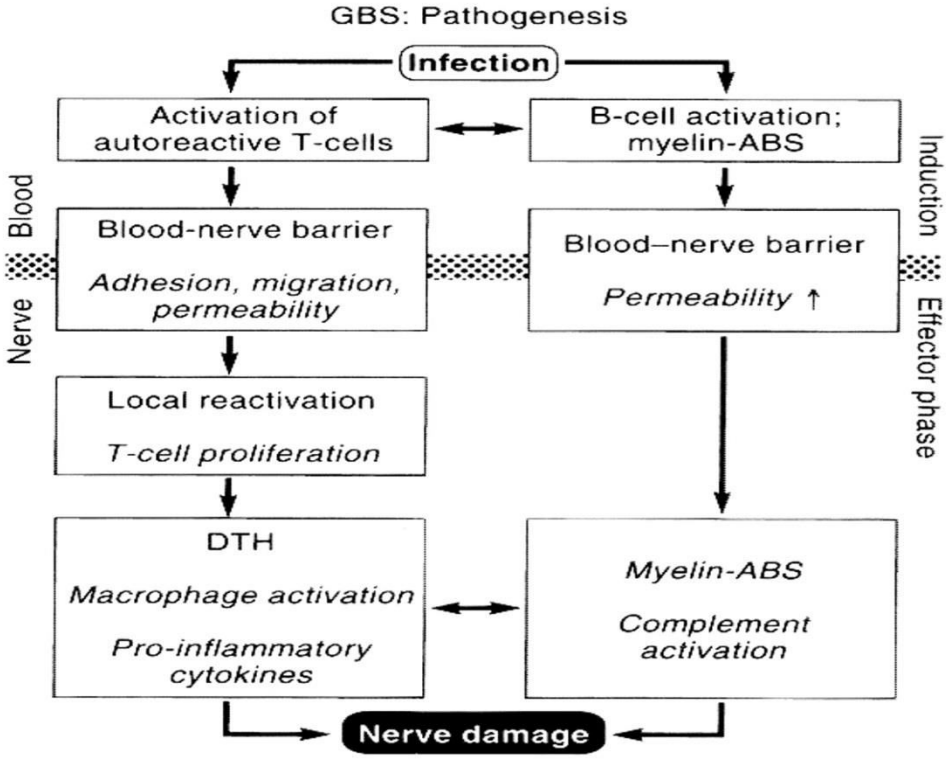
- Guillain-Barré syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature.
- Affects people of all ages.
- Not hereditary.
- Primarily demyelination but sometimes axonal degeneration may occur
- 1-4 cases per 100,000 per year in US (5000-6000/ y).

- Males are at slightly higher risk for GBS than females, and in Western countries adults are more frequently affected than children.

Pathophysiology:







- **In the demyelinating → conduction block.**
  electrophysiologically, (delayed) axonal connections remain (intact).
- **In severe cases of demyelinating GBS → secondary axonal degeneration → slower rate of recovery and a greater degree of residual disability.**
- **Severe primary axonal pattern** → axons have degenerated disconnected from their target → neuromuscular junctions, and must therefore regenerate for recovery to take place.
- **In motor axonal** cases in which recovery is rapid, the lesion is thought to be localized to preterminal motor branches, allowing regeneration and reinnervation to take place quickly.

- **Mild** cases, collateral sprouting and reinnervation from surviving motor axons near the neuromuscular junction may begin to reestablish → several months.

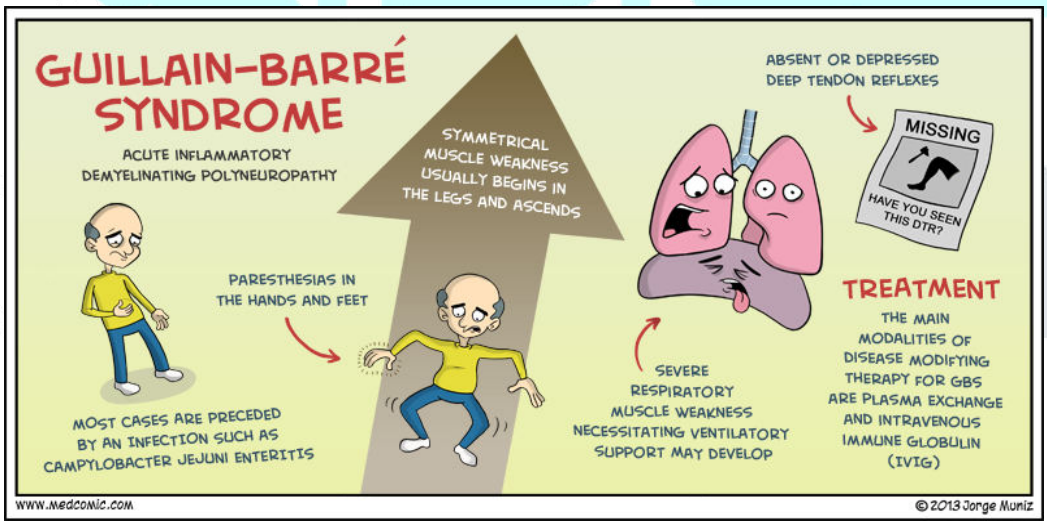
Antecedent Events

1. **75%** of GBS cases are preceded **1-3wks** by an acute infectious process
2. Usually GI or respiratory
3. Campylobacter jejuni
4. Mycoplasma Pneumonia
5. Viral infections : CMV, EBV, HSV
6. Recent Immunization :
   - Swine influenza vaccine
   - Older types of rabies vaccines

7.Usual associations :

- Hodgkin's lymphoma
- HIV+ve pts
- SLE

Clinical manifestations:



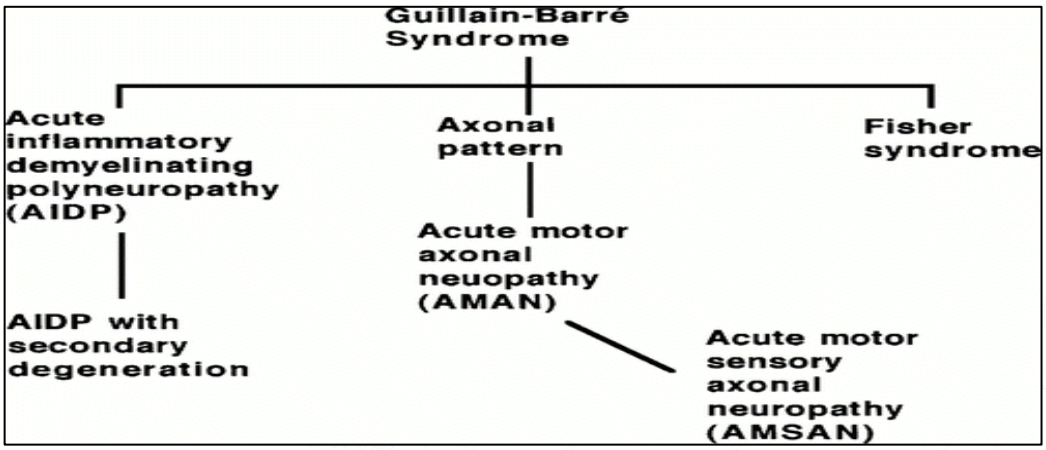
- Rapidly evolving are flexic motor paralysis with or without sensory disturbances
- Ascending paralysis is noticed as rubbery legs
- Weakness evolves over hours to few days
- LL > UL
- 50% have facial di-paresis
- Lower CN are frequently involved (bulbar), causing difficulty in handling secretions and maintaining airways
- Fever and constitutional symptoms are absent (if present re-consider the D_x)
- Sensory deficit can be present (proprioception and deep tendon reflexes > pain& temp.)
- Bladder dysfunction may occur (transient)

- Autonomic involvement may occur
    - Fluctuation in BP
    - Cardiac arrhythmias
    - Postural hypotension

In severe cases Autonomic is common

- Pain is a common feature (deep and aching in weakened muscles, back pain) – self-limited

Clinical subtypes:



1.Acute inflammatory demyelinating polyneuropathy (AIDP)

- Adults affected more than children; 90% of cases in western world.
- rapid recovery.
- anti-GM1 antibodies (<50%)

Demyelination :

- First attack on Schwann cell surface with widespread myelin damage , macrophage activation, and lymphocytic infiltration.
- variable secondary axonal damage

2.Acute motor axonal neuropathy (AMAN)

- Children and young adults.
- prevalent in China and Mexico.
- may be seasonal.
- Rapid recovery.
- anti-GD1a antibodies

Axon :

- First attack at motor nodes of Ranvier with macrophage activation, few lymphocytes and frequent periaxonal macrophages.
- extent of axonal damage highly variable.

3.Acute motor sensory axonal neuropathy (AMSAN)

- Mostly adults .
- Uncommon.
- Slow recovery ,often incomplete.
- closely related to AMAN

Axon :

- Same as AMAN, but also affects sensory nerves and roots. -- axonal damage usually severe

4.Miller-Fisher syndrome(~5% of GBS)

- Acute ophthalmoplegia
- Areflexia, w/o weakness
- Papilledema, pupillary paralysis
- +ve anti-GQ1b Ab

5.Pure sensory form

6.Ophthalmoplegia

7.Bulbar and facial GBS (a/w CMV, anti-GM2 Ab)

8.Acute pandysautonomia.

Clinical course

- Usually benign.
- Spontaneous recovery begins within 2-3wks.
- Most pts. Regain full muscular strength, but some may have residual weakness.
- Tendon reflexes are last to recover.
- Improvement of weakness progresses for bulbar function downward.
- Death may occur if recognized late
- Poor prognostic signs :
  - CN involvement.
  - Intubation.
  - Maximum disability at presentation.

- 7% of children with GBS may have relapse.
- Chronic form (variants)of GBS may be present in some pts. called:
  - Chronic Relapsing Polyradiculopathy OR
  - Chronic Inflammatory demyelinating polyradiculopathy OR
  - Chronic unremitting polyradiculopathy

Congenital GBS

- Rare.
- Generalized hypotonia, weakness and areflexia in neonates.
- Full electrophysiological and CSF criteria are met, in the absence of maternal neuromuscular disease.
- Gradual improvement over the first few months.
- No evidence of residual disease.

Investigations

1. CSF findings :

- Protein is elevated >2x the upper limit(100-1000 mg/dL)
- <10 WBC/mm3
- Glucose is normal
- Culture is negative

2. Motor nerve conduction is severely reduced (EMG studies).

3. CK mildly elevated or normal.

4. Anti-gangliosides Ab (anti-GM1 and anti-GD1) If +ve indicates axonal injury

5.Muscle biopsy not usually required: If done : may be normal, or may show denervation atrophy

6.Sural nerve biopsy may show segmental demyelination, focal infl. And wallerian deg.

7.Serological tests for C.jejuni may be +ve

Diagnosis:

- CSF : Inc protein, Acellular, Normal
- Clinical symptoms
- EMG and NCV: Delayed or blocked

Diagnosis criterias

A.Required for Diagnosis:

1. Progressive weakness of variable degree from mild paresis to complete paralysis.
2. Generalized hypo- or areflexia.

B. Supportive of Diagnosis

1. *Clinical Features:*

   a) Symptom progression: Motor weakness rapidly progresses initially but ceases by 4 weeks. Nadir attained by 2 weeks in 50%, 3 weeks 80%, and 90% by 4 weeks.
   b) Demonstration of relative limb symmetry regarding paresis.
   c) Mild to moderate sensory signs.
   d) Frequent cranial nerve involvement: Facial (cranial nerve VII) 50% and typically bilateral but asymmetric; occasional involvement of cranial nerves XII, X, and occasionally III, IV, and VI as well as XI.
   e) Recovery typically begins 2–4 weeks following plateau phase.

f) Autonomic dysfunction can include tachycardia, other arrhythmias, postural hypotension, hypertension, other vasomotor symptoms.
g) A preceding gastrointestinal illness (e.g., diarrhea) or upper respiratory tract infection is common.

2. Cerebrospinal Fluid Features Supporting Diagnosis

a. Elevated or serial elevation of CSF protein.
b. CSF cell counts are <10 mononuclear cell/mm^3.

3. Electrodiagnostic Medicine Findings Supportive of Diagnosis

a. 80% of patients have evidence of NCV slowing/conduction block at some time during disease process.
b. Patchy reduction in NCV attaining values less than 60% of normal.
c. Distal motor latency increase may reach 3 times normal values.
d. F-waves indicate proximal NCV slowing.
e. About 15–20% of patients have normal NCV findings.
f. No abnormalities on nerve conduction studies may be seen for several weeks.

C. Findings Reducing Possibility of Diagnosis

1. Asymmetric weakness.
2. Failure of bowel/bladder symptoms to resolve.
3. Severe bowel/bladder dysfunction at initiation of disease.
4. Greater than 50 mononuclear cells/mm3 in CSF.
5. Well-demarcated sensory level.

D.Exclusionary Criteria

1. Diagnosis of other causes of acute neuromuscular weakness (e.g., myasthenia gravis, botulism, poliomyelitis, toxic neuropathy).
2. Abnormal CSF cytology suggesting carcinomatous invasion of the nerve roots

Differential Diagnosis

- Myelopathies: prolonged back pain and sphincter disturbances .
- Botulism: pupillary reflex lost early.
- Diphtheria: early oropharyngeal disturbances.
- Lyme polyradiculopathy.
- Vasculitic neuropathy: inc. ESR.
- Polio: fever and meningism.
- CMV polyradiculitis: immunocompromised.
- Neuromuscular disorders.

Treatment

- 2 weeks after the first motor symptoms, it is not known whether immunotherapy is still effective.
- If the patient has already reached the plateau stage, then treatment probably is no longer indicated, unless the patient has severe motor weakness and one cannot exclude the possibility that an immunologic attack is still ongoing.

- Either high-dose intravenous immune globulin (IVIG) or plasmapheresis can be initiated, as they are equally effective for typical GBS .
  A combination of the two therapies is not significantly better than either alone.

1. **IVIg** is often the initial therapy chosen because of its ease of administration and good safety record. Anecdotal data has also suggested that IVIg may be preferable to PE for the AMAN and MFS variants of GBS.
   - IVIg is administered as five daily infusions for a total dose of٢ g/kg body weight .

2. Plasmapheresis usually consists of 40-50 mL/kg plasma exchange (PE (four to five times over a week.
   - Meta-analysis of randomized clinical trials indicates that treatment reduces the need for mechanical ventilation by nearly half (from 27%to 14% with PE) and increases the likelihood of full recovery at 1year(from 55%to 68%)
   - Functionally significant improvement may occur toward the end of the first week of treatment, or mabe delayed for several weeks .

- The lack of noticeable improvement following a course of IVIg or PE is not an indication to treat with the alternate treatment .
- There are occasional patients who are treated early in the course of GBS and improve, who then relapse within a month
- Brief retreatment with the original therapy is usually effective in such cases.
- Glucocorticoids have not been found to be effective in GBS.
- Occasional patients with very mild forms of GBS, especially those who appear to have already reached a plateau when initially seen, may be managed conservatively without IVIg or PE.

In the worsening phase of GBS

most patients require monitoring in a critical care setting, with particular attention to vital capacity, heart rhythm, blood pressure, nutrition, deep vein thrombosis prophylaxis, cardiovascular status ،early consideration (after 2 weeks of intubation) of tracheotomy, and chest physiotherapy .

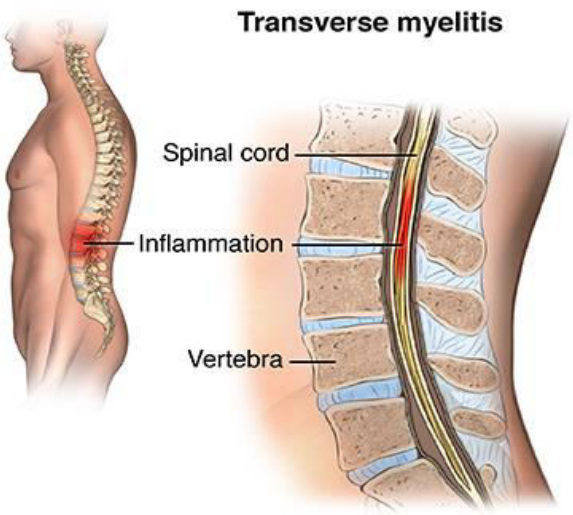
- As noted 30 %of patients with GBS require ventilatory assistance ،sometimes for prolonged periods of time (several weeks or longer)
- Frequent turning and assiduous skin care are important, as are daily range-of-motion exercises to avoid joint contractures and daily reassurance as to the generally good outlook for recovery.

Prognosis and Recovery

- Approximately 85% of patients with GBS achieve a full functional recovery within several months to a year.
- Areflexia may persist and patients often complain of continued symptoms, including fatigue.
- The mortality rate is <5% in optimal settings; death usually results from secondary pulmonary complications.
- The outlook is worst in patients with severe proximal motor and sensory axonal damage.
- Axonal damage may be either primary or secondary in nature but in either case successful regeneration cannot occur.
- advanced age, a fulminant or severe attack, and a delay in the onset of treatment Risk incr

- Between 5 and 10% of patients with typical GBS have one or more late relapses; such cases are then classified as chronic inflammatory demyelinating polyneuropathy (CIDP).

Transverse Myelitis



- Is a neurological disorder caused by an inflammatory process of the spinal cord, and can cause axonal demyelination.

- Transverse implies that the inflammation is across the thickness of the spinal cord.

- Abrupt onset of progressive weakness and sensory disturbances in LL.

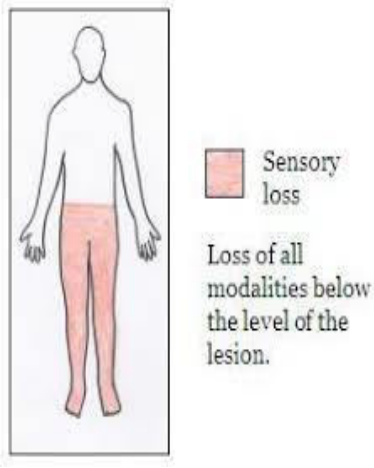
- Mostly they have a history of preceding viral infection, fever and malaise : EBV, HSV, Influenza, rubella, mumps, varicella
  Others: M.pneumonia, Lyme disease, schistosomiasis

Pathophysiology

- 3 hypothesis:
  - Cell-mediated autoimmune response
  - Direct viral invasion
  - Autoimmune vasculitis , and insufficient blood flow through spinal cord vessels.

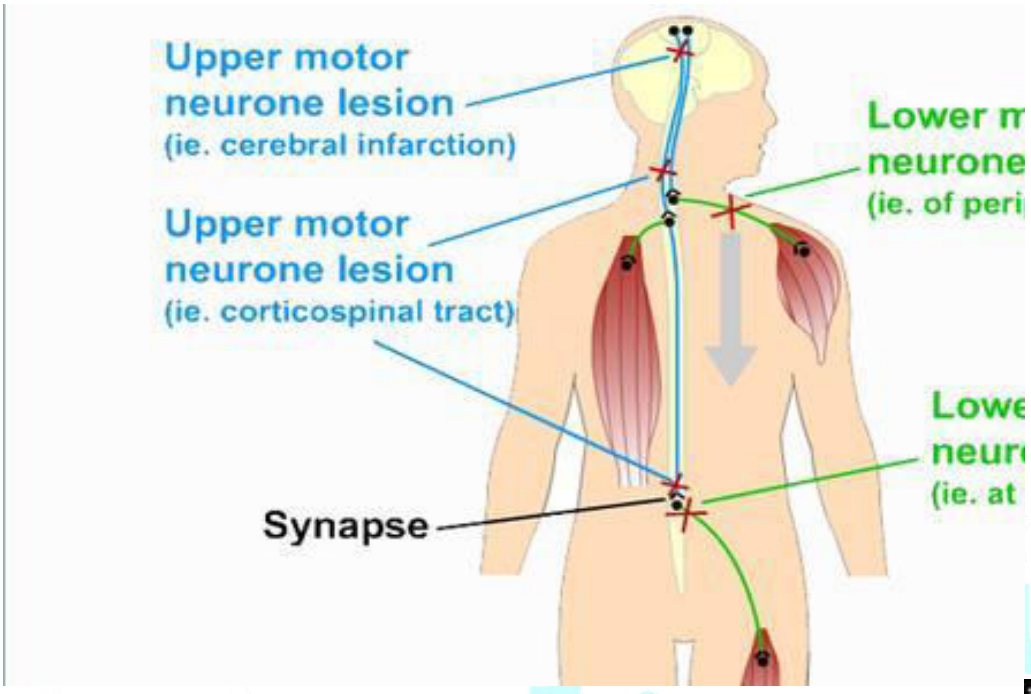
Clinical manifestations

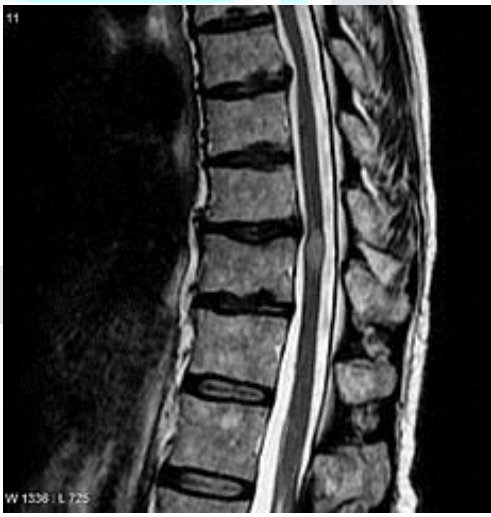
- With acute transverse myelitis, the onset is sudden and progresses rapidly in hours and days.
- The symptoms and signs depend upon the level of the spinal cord involved and the extent of the involvement of the various long tracts.
- LL weakness or paralysis
- Low back or abdominal pain
- Paresthesia of LL is the prominent feature
- Sensory level of impairment is usually present (mid-thoracic region)
- Pain, temp. and light touch are affected
- Proprioception and vibration may be preserved
- Bladder paralysis often occurs and urinary retention is an early manifestation.
- Fever and nuchal rigidity early in the course of disease
- Neurological deficit evolves over 2-3 days then plateaus, with flaccidity changing to spasticity and emerging of UMNL signs in LL
- signs of spinal shock may be evident, in which the lower limbs will be flaccid and areflexic, rather than spastic and hyper-reflexic as they should be in upper motor neuron paralysis



► If the upper cervical cord is involved, all four limbs may be involved and there is risk of respiratory paralysis (segments C3,4,5 to diaphragm).

- Lesions of the lower cervical (C5–T1) region will cause a combination of upper and lower motor neuron signs in the upper limbs, and exclusively upper motor neuron signs in the lower limbs.
- A lesion of the thoracic spinal cord (T1–12) will produce upper motor neuron signs in the lower limbs, presenting as a spastic diplegia.
- A lesion of the lower part of the spinal cord (L1–S5) often produces a combination of upper and lower motor neuron signs in the lower limbs.





Investigations

- CSF analysis :
  - Moderate lymphocyte pleocytosis
  - Normal or slightly elevated protein
- CT/MRI :
  - May show fusiform swelling in the affected region (3-4 vertebral levels)
  - Mainly to r/o compressive lesions

Management

- Management is supportive
- Management is directed to bladder care and physiotherapy.
- Studies have shown that high-dose methylprednisolone therapy early in the course is effective in shortening the duration of the disease and in improving the outcome.

Outcome

- Recovery from transverse myelitis usually begins between weeks 2 and 12 following onset and may continue for up to 2 years in some patients.
- 60% show spontaneous recovery over few weeks
- if treated early, some patients experience complete or near complete recovery.
- Residual deficits includes bowel and bladder dysfunction and weakness.

Spinal muscular atrophy

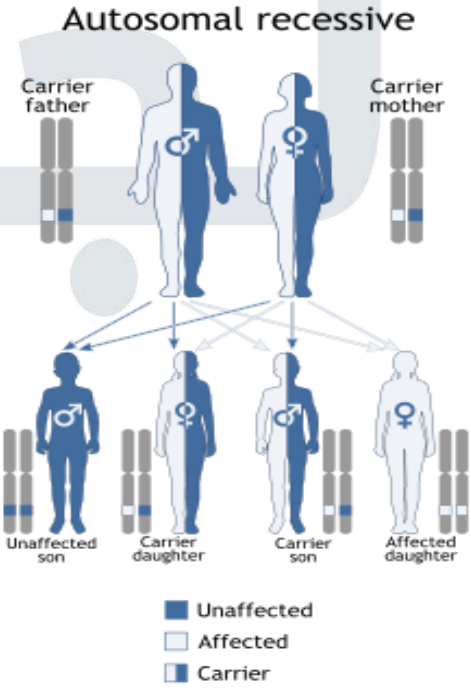
- Is an incurable genetic autosomal recessive disease caused by a genetic defect in the SMN1 gene which codes SMN, a protein necessary for survival of motor neurons.

- Resulting in death of neuronal cells in the anterior horn of spinal cord and subsequent system-wide muscle wasting (atrophy).

- manifests in various degrees of severity which all have in common general muscle wasting and mobility impairment.

- Sensation, which originates from the posterior horn cells of the spinal cord, is spared, as is intelligence. Several muscles are spared, including the diaphragm , EOM, the involuntary muscles of the gastrointestinal system, the heart, and the sphincters.

Causes



- The SMN1 gene chromosome 5 is mutated so unable to code the SMN protein - due to either a deletion occurring at exon 7 or to other point mutations (frequently resulting in the functional conversion of the SMN1 sequence into SMN2).

- All patients, however, retain at least one copy of the SMN2 gene which still code small amounts of SMN protein around 10-20% of the normal level allowing neurons to survive.

- ► Muscles of lower extremities are usually affected first, followed by muscles of upper extremities, spine and neck and, in more severe cases, pulmonary and mastication muscles.
- ► Proximal muscles are always affected earlier and in a greater degree than distal.

Types:

SMA manifests over a wide range of severity affecting infants through adults. The disease spectrum is variously divided into 3–5 types, in accordance either with the age of onset of symptoms or with the highest attained milestone of motor development.

- Type I (Werdnig-Hoffmann disease):
  This acute infantile SMA is usually identified in patients from birth to age 6 months.

- Type II: This chronic infantile SMA is diagnosed in infants aged 6-12 months.

- Type III (Kugelberg-Welander disease):
  This type of SMA is diagnosed in children aged 2-15 years.

**The severity of SMA smptoms is broadly related to how well the remaining SMN2 genes can make up for the loss of SMN1, while SMA II and III patients usually have at least three SMN2 copies; and SMA IV patients normally have at least four of them.

History

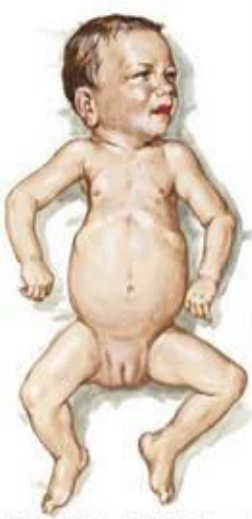
- Type I: Most mothers report abnormal inactivity of the fetus in the latter stages of pregnancy. The patient is unable to roll over or sit. Progressive clinical deterioration occurs. Death usually occurs from respiratory failure and its complications in patients by age 2 years.

- Type II: Patients have normal development for the first 4-6 months of life. They may be able to sit independently, but they are never able to walk. They require a wheelchair for locomotion. Nasal speech and problems with swallowing develop later. Scoliosis becomes a major complication in many patients with long survival . They have a longer life span than patients with type I SMA.

- Type III: the presenting complaint is difficulty climbing stairs or getting up from the floor (due to hip extensor weakness). The life span is nearly normal.

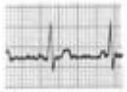
Signs & Symptoms

- The symptoms vary greatly depending on the SMA type involved, the stage of the disease and individual factors and commonly include:
- Areflexia, particularly in extremities.
- Overall muscle weakness, poor muscle tone, limpness or a tendency to flop (the "floppy baby" syndrome).
- In infants: adopting of a frog-leg position when sitting (hips abducted and knees flexed).
- Difficulty achieving developmental milestones, difficulty sitting/standing/walking.
- Signs & Symptoms
- Loss of strength of the pulmonary muscles: weak cough, weak cry (infants), accumulation of secretions in the lungs or throat, respiratory distress.
- Bell-shaped torso (caused by using only abdominal muscles for respiration)
- Clenched fists with sweaty hands
- Head often tilted to one side, even when lying down
- Fasciculations (twitching) of the tongue
- Difficulty sucking or swallowing, poor feeding
- Arthrogryposis (multiple congenital contractures)
- Weight lower than normal



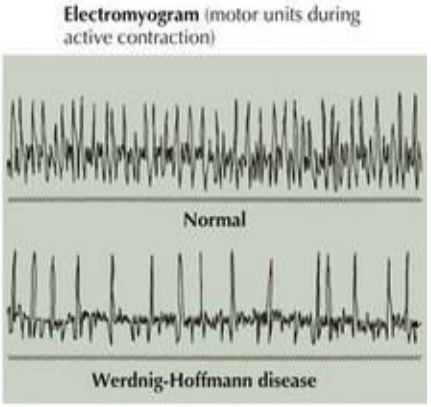
Infant with typical bell-shaped thorax, frog-leg posture, and "jug-handle" position of upper limbs

Muscle biopsy specimen showing groups of small atrophic muscle fibers and areas of normal or enlarged fibers (group atrophy) (trichrome stain).



Baseline tremor in otherwise normal electrocardiogram

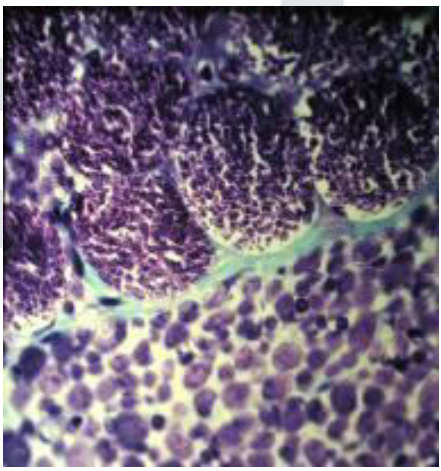
Boy with much milder, late-onset form of disease (Kugelberg-Welander disease). Marked lordosis and eversion of feet



Diagnosis

- Prenatal screening is controversial, because of its cost
- Very severe SMA (type I) can be sometimes evident before birth - reduction in fetal movement in the final trimester.
- Further, for all SMA types:

1. Patient will present with hypotonia associated with hyporeflexia.
2. Results of motor nerve conduction studies are normal, except for mild slowing in terminal stages of the disease, an important feature distinguishing SMA from peripheral neuropathy.
3. Electromyogram will show fibrillation and muscle denervation
4. Serum creatine kinase may be normal or increased
5. Genetic testing will show bi-allelic deletion of exon 7 of the SMN1 gene – this is conclusive of the disease.

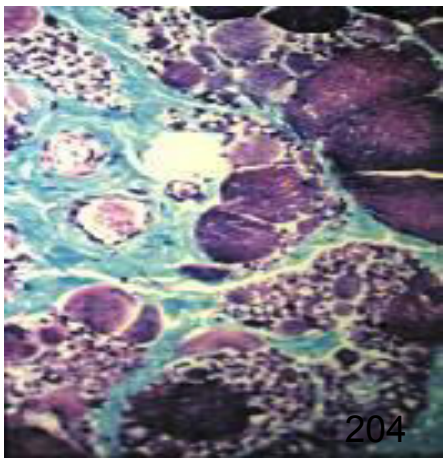


Histological findings

- Spinal muscle atrophy, Werdnig-Hoffman disease.
- Groups of giant type I fibers are mixed with fascicles of severely atrophic fibers
- Kugelberg-Welander disease. Marked variation in muscle fiber size along with increased perimysial connective tissue.

Treatment

- Care is symptomatic
- Orthopaedics
- Respiratory care
- Nutritional care
- Mobility — Assistive technologies



- Mental health — SMA children do not differ from the general population in their behaviour; their cognitive development can be slightly faster, and certain aspects of their intelligence are above the average.

Prognosis

- The younger the patient is at onset, the worse the prognosis is.
- Patients with type I spinal muscle atrophy usually die by age 2 years.
- Patients with type III SMA have nearly normal life expectancy.
- Death occurs as a result of respiratory compromise. The life span of affected individuals has significantly increased with the use of intermittent positive pressure ventilation with or without a tracheostomy.
- Patient Education
- Prenatal diagnosis in the first trimester and proper genetic counseling are possible with DNA analysis. This enables more accurate carrier detection. Not all parents of children with spinal muscle atrophy are obligate carriers.
- Carrier testing is important for reproductive decision-making. 3% of cases are sporadic.

Child abuse

- Child abuse (including neglect) is any form of maltreatment of a child, either by inflicting harm or by failing to act to prevent harm.
- Children may be abused in a family, institutional, or community setting, by those close to them, such as a parent or caregiver or, more rarely, by a stranger. They may be abused by adults or by other children.

- There are 4 categories of child abuse:
  - ► physical abuse
  - ► emotional abuse (also called psychological maltreatment),
  - ► sexual abuse,
  - ► Neglect.

Epidemiology

- Child abuse is a worldwide phenomenon and can affect children of all ages; however, the highest incidence occurs to infants and toddlers
- It is difficult to gain a true estimate of child abuse due to the hidden nature of the problem.
- *In industrialized countries it is estimated that :*
  4% to 16% of children are physically abused, around 10% are neglected (emotionally abused), 5% of boys and 5% to 10% of girls are exposed to penetrative sexual abuse, and 30% are exposed to any form of sexual abuse. Around 80% of child abuse is perpetrated by caregivers or parents

Etiology

There is no specific etiologic factor of child abuse; causes and risk factors are multifactorial

- Parental (or caregiver) risk factors
  1. Poor socioeconomic status (e.g., poverty, low income, and/or an economic crisis within the family).
  2. inadequate child care and poor parental education.
  3. Psychological problems such as depression, stress, or other mental health problems of a caregiver may expose the child to abuse.
  4. Substance abuse may inhibit the caregiver's ability to recognize the needs of the child, contributing to neglect, and may cause financial hardship.
  5. Unmet emotional needs on the part of the parent or caregiver may predispose toward neglect of a child
  6. Lack of parenting knowledge may lead to unrealistic expectations of the child
  7. Parental or caregiver exposure to maltreatment as a child is a risk factor for child abuse, with evidence of a pattern of abuse running through generations in some families.

  ❖ This is thought to be due to sex role stereotypes and a repetition of a pattern of violence
- Child risk factors
  1. Children with mental or physical health problems.

2. Children with disabilities have been noted to be twice as likely to be abused as nondisabled children,although maltreatment also contributes to disabilities.
3. Low birth weight
4. Excessive crying and/or frequent tantrums have been associated with abusive head trauma•
5. Twins

Classification

Classification by type of abuse

- Physical abuse May involve causing physical harm by hitting, shaking, burning, smothering, poisoning, biting, or throwing the child.
- Injuries sustained by physical abuse may include bruises, fractures, burns, oral injuries, bites, head and spinal injuries, and abdominal injuries.
- The challenge for the clinician is to distinguish inflicted injuries from accidental injuries.

- Emotional abuse This may involve conveying to the child that they are worthless, unloved, inadequate, or valued only as long as they meet the needs of another person. Overprotection and limitation of exploration and learning, or preventing the child from participating in normal social interaction.
- Any serious bullying, causing a child to feel frightened or in danger, or the exploitation of the child.
- Some level of emotional abuse is involved in all types of maltreatment of a child.

- Sexual abuse involves forcing or enticing a child or young person to take part in sexual activities, including prostitution and pornography, whether or not the child is aware of what is happening
- Activities may involve physical contact, including penetrative or non-penetrative acts
- Actions may include noncontact activities, such as involving children in the viewing or production of sexual images or encouraging children to behave in sexually inappropriate ways.

- Neglect is the failure to meet the basic physical and/or psychological needs of a child, It may also include neglect of, or unresponsiveness to, the basic emotional needs and includes failure to Provide adequate food, clothing, and shelter (including exclusion from home or abandonment)
- Protect a child from physical and emotional harm or danger • Ensure adequate supervision (including the use of inadequate caregivers)
- Ensure access to appropriate medical care or treatment.
- Neglect may also occur during pregnancy as a result of the mother failing to consider the developing needs of the child.

Step-by-step diagnostic approach

- Injuries caused by physical abuse such as bruising, fractures, oral injuries, bites, head and spinal injuries, abdominal injuries, and burns challenges the clinician to distinguish inflicted injuries from those that have occurred accidentally. Finding one or more of the above injuries in a child requires a full further evaluation for other injuries typical of abuse.
- Some markers currently used to identify children who should be assessed further for possible abuse or neglect (e.g., repeated presentation, age, injury type

- clinical prediction rule, **the TEN-4 rule**, is highly specific and sensitive for identifying high-risk bruising that requires an abuse work up

- A bruise on a child's torso, ears, neck, or any part of the body of an infant <4 months old (TEN-4) should trigger an abuse evaluation

History suggestive of nonaccidental injury (NAI)

1. A history of trauma inconsistent with the injuries, a changing history, unexplained coexistent injuries, or previous history of injuries.

2. Injuries that do not fit with the developmental age of the child (if children are not yet independently mobile, they unlikely to fall against certain objects). Details of the mechanism of injury may help determine whether the explanation is compatible with the injury and the developmental level of the child.

3. Faltering growth or failure to thrive

4. Poor parent-child bonding. Parental attempts at excusing or justifying the injury inappropriately or blaming a younger sibling or pet

- To exclude non abusive causes, the clinician should take:

1. perinatal history (birth-related trauma) 2.prematurity,
3.physical therapy and medications
4.iatrogenic causes
5. Past medical history of fractures or bleeding disorders.

- Questions about family history of fractures and deafness can help too
- It is important to ask about all relevant information about the child's family/caregivers (attendance in primary or secondary care, registration with social services,. Any history of drug dependency or previous convictions should be noted

Head injuries

- Abusive head trauma (AHT) is the most common cause of fatal physical abuse
- Presenting features range from severe neurologic compromise (coma) to symptoms such as seizures, lethargy, irritability, vomiting, poor feeding, and increasing head circumference.

► How to Distinguishing AHT VS accidental head trauma??
Interpretation of the history and the presenting signs and symptoms

Markers of AHT

- Subdural hemorrhages in children <1 year old
- Bilateral or interhemispheric subdural hemorrhages
- Significant head injury with no explanation of trauma, or with an explanation involving a low fall less than 5 feets

- Coexisting apnea or other form of acute respiratory compromise[
- Coexisting bruising to the head or neck or torso
- Retinal hemorrhages
- Rib or long bone fractures
- Skull fractures other than a simple linear parietal skull fracture
- Seizure without prior history of seizure disorder or fever

► Retinal hemorrhages in multiple retinal layers and extending to the periphery is highly specific for AHT, and it is seen in approximately 85% of cases
► few retinal hemorrhages confined to the posterior pole is regarded as nonspecific
► other medical causes of retinal hemorrhages (birth, coagulation disorders, carbon monoxide poisoning)
► Infants <6weeks of age may have minor retinal hemorrhages following birth, particularly after an instrumental delivery

► Subdural hemorrhages are the most common intracranial injury seen in AHT, and may occur in combination with other extra-axial hemorrhages or injuries to the brain itself. Physical abuse is the most common cause of subdural hemorrhage in children less than 1 year old
*are typically small and multiple
*They occur commonly over the convexity and in the intrahemispheric fissure.[
*They may have different or mixed densities on CT or MRI
► ***Epidural hemorrhages, however, are more commonly seen with accidental head trauma

Spinal injuries

- spinal injuries are uncommon in children with physical abuse
- if it happens it would be masked with the loss of consciousness a combined with the AHT
  e.g Unstable spinal fractures such as hangman's fracture#
- Cervical spine in younger infants (mean age 5 months) or in the thoracolumbar spine in older toddlers (mean age 14 months

Presentation :

1. bony tenderness over the site of the vertebral
2. specific neurologic signs, such as paraplegia, quadriplegia, incontinence, or absent sensation below the level of cord injury.
3. Unexplained kyphosis in an older child should also raise a suspicion of previous abuse

Abdominal injuries

They are predominantly seen in children <5 years

1. no specific history of trauma to the abdomen
2. present with nonspecific symptoms (nausea, vomiting, loss of consciousness, and/or an acute abdomen)
3. Frequently, there is a delay in seeking care
4. Abdominal injuries may occasionally be masked by symptoms and signs of head injury

- most specific abdominal injuries as a consequence of abuse are hollow viscus injuries (e.g., small bowel and splenic injury)
- Solid organs injuries happens in both accidents and abuse
- Abdominal bruising is rare
-

Fractures

- Rib fractures are the strongest predictors of child abuse in infants in the absence of major trauma or pathologic causes, and are due to either the squeezing of the chest or a direct blow
- Fractures of long bones in premobile children are very worrying for abuse but can be seen in accidental injury. The history given by caregivers should be consistent with a fracture mechanism in the accidental injury
- Classic metaphyseal lesions (called corner fractures, bucket handle fractures) are highly specific for abuse in infants under 1 year of age These fractures occur from vigorous pulling, or twisting of an extremity
- Supracondylar fractures of the humerus are far more common in accidental falls
- Simple linear skull fractures are equally prevalent in abusive and nonabusive injuries

Oral injuries

- The most common oral injuries described are bruising or lacerations to the lips
- The mouth should be fully examined, and any missing or abnormal teeth recorded.

Torn frenum (or frenulum):

- When it is associated with severe or injuries (head injury) and unexplained bruising to the cheeks, ears, neck, or trunk should raise concern for **abuse, it** may occur by force-feeding an infant, although it has only conclusively been reported following a direct blow It is accompanied by a lot of apparent bleeding (mixed saliva and blood).
- When isolated (excluded any other injury) cannot be assumed to be abusive. It may occur accidentally, from a direct blow (swing hitting mouth, fall onto face, sport injury).
  *Torn frenum has been described during attempted intubation.

Dental injuries

- Abusive dental injuries include forced intrusions, extrusions, removal of healthy secondary teeth, and microfractures
- Parents have been known to forcefully extract a child's healthy teeth as a "punishment."
- Up to 50% of children with dental injuries sustain them accidentally, from falls or sports injuries
- Grayish discoloration of the teeth may also occur with dentinogenesis imperfecta, particularly when associated with osteogenesis imperfecta, a condition resulting in recurrent fractures.
- + dental neglect

Bruising

Bruising is one of the most common accidental injuries that children sustain during normal day-today activities. However, bruising is also the most common manifestation of physical abuse

Accidental	Non–accidental
mobile children on the front of the body and over bony prominences	head and face is the most common site of bruising,back, buttocks, forearm, cheeks , ears, abdomen or hip, upper arm, posterior leg, foot, or hand.[
head brusis are commonly found over the forehead, nose, upper lip, or chin	TEN–4
	occur in clusters /defensive injuries (outside of the forearm and thighs may reflect patterned image of the object used (belt buckle, dog collar) or it may be associated with abrasions (in rope injury).
	More numerous Petechial association

Bites

- Bites to children may be seen with both accidental injuries (e.g., child-to-child bites among toddlers) and abusive injuries.
- Abusive bites may occur in younger children on the arms, legs, back, shoulders, and buttocks
- Adolescents who are the victims of sexual abuse may be bitten over the breasts and neck, as in adult attacks.
- Distinguishing child bites from adult bites is challenging. Any bite with an intercanine distance of >3 cm is more likely to be from an adult; an intercanine distance of
- Children are sometimes bitten by animals: most commonly dogs, cats, and ferrets. Animal bites are usually tearing injuries

Poisonings

accidental	Non accidental
•ingestion of small amounts of domestic products or medications.	•large quantities of a substance have been ingested
•The child is presented promptly by the parents or caregivers,	•or if there is no history or a history of ingestion of small amounts of poison inconsistent with the clinical presentation.
•able to give a history of ingestion or of the child being found in the proximity of an opened container of poison	• The most common agents of intentional poisoning include drugs prescribed for family members

*Frequent presentations with “accidental" ingestion should raise the suspicion of parental negligence

Burns

- The most common burns in childhood, both abusive and accidental, are scalds

	accidental	Non accidental
Distribution:	face, head, neck, upper trunk, and 1 upper limb	the lower extremities, with or without the buttock or perineum "**doughnut" sign
Pattern	mixed depth, superficial to partial-thickness, with the deepest burn at the first site of contac	depth is often uniform, with partial- or full-thickness burns
outline	irregular, without clear margins	and clear margins
Extent	varies based on the quantity of liquid involved and the speed first aid given.	extensive, involving a large total body surface area,

- Immersion injuries and are most commonly caused by hot water

Contact and caustic burns

- contact burns are the most common non scald burn described in abuse.
- They are most frequently noted on the back, shoulders, and buttocks; are usually clearly demarcated; and in some cases can be precisely matched to the burn agent (cigarette lighter
- Accidental contact burns to the hands are common in toddlers, typically from grabbing items such as hot stoves.
- Inflicted cigarette burns are circular, full thickness, in areas where the child is unlikely to receive an accidental burn
- Accidental cigarette burns are superficial, may leave no pattern or a cone-shaped mark, and occur on exposed areas of skin.

Risk factors

Strong :

1.domestic violence

2.substance abuse/mental health disorder in parent/caregiver

3.excessive crying and/or frequent tantrums in infancy

4.lack of maturity/poor coping skills in parent/caregiver

5.parent/caregiver abused as a child

Weak

- poor socioeconomic status

- demanding parenting role

History & examination factors:

Key diagnostic factors

1.inconsistent/changing history (common)

2.unexplained/inconsistent injuries in isolation or in combination

3.bruising

4.subdural hemorrhages in an infant/young toddler

5.long bone fractures in a premobile child

6.multiple fractures of different ages and bilateral fractures
(Multiple fractures of differing ages are very indicative of multiple episodes of inflicted trauma. Bilateral fractures in children are also commonly a result of inflicted trauma)

7.rib fractures in the absence of major trauma or pathologic causes

8.immersion scalds

9.small bowel perforation in a child

10.torn frenum (uncommon)

11. poor parent–child bonding

12.faltering growth

13.dental neglect

14.petechiae with bruising

15.extensive, multilayered retinal hemorrhages extending to periphery

16. apnea

• Coexisting apnea or some other form of acute respiratory compromise should prompt concern for an abusive head trauma

17.cigarette burns

18.frequent accidental poisonings

19.contact burns

20.dental injuries

caustic burns

Diagnostic tests:

1st test to order:

- Cbc:

- Excludes some platelet abnormalities as a cause of bruising
- identifies other hematologic abnormalities (e.g., leukemia)
- Highlights presence of anemia or blood loss.

- Clotting profile:

- Excludes many clotting abnormalities as a cause of bleeding and bruising.
- Result: normal Mild abnormalities may be present in head trauma

- **Dilated funduscopy** : retinal hemorrhages
- **Photo documentation of injuries**
- **Skeletal survey** : fractures on X-RAY
- **Ct brain:**
  - subdural hemorrhage,
  - subarachnoid hemorrhage,
  - complex skull fractures,
  - parenchymal injury
  - cerebral edema

- **LFTs/amylase:** elevated alt and ast and amylase
- **Serum calcium**: normal
- **Serum phosphate :**normal
- **Serum alkaline phosphatase** :may be elevated due to fractures
- **Serum parathyroid hormone :**normal
- **Serum 25-hydroxyvitamin D :**normal

Other tests to consider:

- **radionuclide bone scan**: alternative for skeletal survey and appear as hotspot
- **MRI brain/spine** :subdural hemorrhage, Subarachnoid hemorrhage, parenchymal injury, cerebral edema, hypoxic-ischemic injury, diffuse axonal injury, and spinal injuries
- **ultrasound abdomen** :free fluid or blood in the abdominal space
- **CT abdomen** : hollow organ rupture, subcapsular hematomas, ruptures of liver or spleen, renal injury
- **platelet function studies and von Willebrand factor assays:** normal
- **x-ray mouth:** dental or mandibular fracture
- **forensic dental referral:** may identify perpetrator
- **forensic swabs for DNA:** may identify perpetrator
- **toxicology testing**: positive for specific agent(s) used

Differential diagnosis

- **Coagulopathy:** CBC, platelet function tests, prothrombin time (PT), prolonged thrombin time, thrombin, fibrinogen, von Willebrand factor and other clotting factor assays help identify the etiology.
- **Osteogenesis imperfecta:** Type I and type IV. Type I frequently has associated blue sclera. Type II (lethal) and type III (severe, progressively deforming) OI: easily diagnosed clinically and radiologically due to the severity
- **Rickets of prematurity:** clinical diagnosis
- **Phytophotodermatitis:** clinical diagnosis
- **Impetigo:** skin swaps
- **Mongolian blue spot:** clinical diagnosis
- **Coining:** linear marks found on the back or chest and diagnosed clinically

Encephalitis

Encephalitis is an inflammation of the brain parenchyma

- Acute Vs Chronic
- Localized Vs Generalized
- (Parenchyma: Encephalitis, Meninges: Meningitis, Both: meningoencephalitis)
- Non – Infectious Vs Infectious
- (Reye syndrome, hypoglycemia, collagen vascular disorders, drugs, hypertension, and malignancies)
- (Viral, Bacterial, Fungal, Ricketssial, Parasitic)

Viral Encephalitis

Causes of acute viral encephalitis:

*** Arboviruses:**

- St. Louis encephalitis virus (Birds)
- Lacrosse encephalitis virus (Mosquitoes)
- Eastern equine encephalitis (Birds & Mosquitoes)
- Western equine encephalitis (Birds & Mosquitoes)
- West Nile encephalitis virus (Mosquitoes)

Enteroviruses

Herpesviruses (HSV, EBV, CMV, VZV)

*** HIV**

*** Influenza viruses**

*** Lymphocytic choriomeningitis virus**

*** Measles virus (native or vaccine)**

*** Mumps virus (native or vaccine)**

*** Rabies virus**

*** Rubella virus**

Pathophysiology:

- In general, the virus replicates outside the CNS and gains entry either by Hematogenous spread or Traveling along neural and olfactory pathways (rabies, HSV, VZV).

- Once across the blood-brain barrier, the virus enters neural cells, leading to:

  . Disruption in cell functioning
  . Perivascular congestion
  . Hemorrhage
  . Inflammatory response diffusely affecting gray matter disproportionately to white matter.
  . Focal pathology is the result of neuron cell membrane receptors found only in specific portions of the brain and accounts for regional tropism found with some viruses.

E.g. HSV has a predilection for the inferior and medial temporal lobes

-Once the virus has entered the bloodstream, it may localize in the brain, causing inflammation of brain tissue and surrounding membranes. White blood cells invade the brain tissue as they try to fight off the infection.

- The brain tissue swells (cerebral edema), which may cause destruction of nerve cells, bleeding within the brain (intracerebral hemorrhage), and brain damage.

Epidemiology:

- It's a rare disease that only occurs in approximately 0.5 per 100,000 individuals

- Most commonly in children, the elderly and immunocompromised patients

- Arboviral and enteroviral encephalitis characteristically appear in clusters or epidemics that occur from summer to early fall.

- Herpes viruses and other infections agents account for additional sporadic cases throughout the year.

Mortality, Morbidity:
affected by :

a. Preexisting CNS injury
b. The virulence of infecting organism

. The overall mortality 5%
. About two thirds of patients recover while one third show clinically significant residua, including : paresis or spasticity, cognitive impairment , weakness , ataxia , and recurrent seizures.

Prognosis (Poor):

a. Eastern equine encephalitis
b. HSV , Mycoplasma
c. <1year age
d. Coma
e. Rabis is fatal

Complications:-

. Seizures
. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
. Increased intracranial pressure (ICP)
. Coma

Clinical Manifestation:

1. Prodrome (Several Days)

* Nonspecific symptoms:

1. fever
2. headache
3. cough
4. sore throat
5. abdominal complaints

* Specific Symptoms (EBV, CMV, measles & mumps):

1. rash
2. lymphadenopathy
3. hepatosplenomegaly
4. parotid enlargement

2. Characteristic Symptoms

. Progressive lethargy
. Behavioral changes
. Neurological deficits
. Seizures
. Maculopapular rash
. Severe complications :

1. Coma
2. Transverse myelitis

Approach

History

- Hx of fever, headache, N & V , lethargy, and myalgias (viralprodrome)
- Hx of rash, lymphadenopathy, hepatosplenomegaly, and parotid enlargement (specific prodrome)****
- Dysuria and pyuria (St Louis encephalitis)
- Extreme lethargy (WNE)
- The **classic presentation** is encephalopathy with diffuse or focal neurologic symptoms, including the following:
  . Behavioral and personality changes, with or LOC
  . Neck pain, stiffness
  . Photophobia
  . Lethargy
  . Generalized or focal seizures
  . Acute confusion or amnestic states

- Flaccid paralysis (10% of patients with WNE)

➢ Symptoms of **(HSV)** infection in *neonates* (aged 1-45 d) include:

1) localized skin, eye, or mouth lesions in the early phase
2) Diminished alertness, irritability, seizures, and poor feeding develop later
3) disseminated disease and shock are late findings.

➢ Herpes simplex encephalitis (HSE) in older *children* and *adults* is not typically associated with active herpetic eruptions and is characterized by the acute onset of more severe symptoms of encephalitis early in the course of illness

Physical examination

❑ Look for supporting evidence of viral infection.

❑ Typical findings include the following:

Altered mental status and Personality changes (MC)

❑ Focal findings, such as : hemiparesis, focal seizures, and autonomic dysfunction

❑ Movement disorders (St Louis encephalitis, [EEE], [WEE]) / Ataxia]

❑ Cranial nerve defects

❑ Dysphagia, particularly in rabies

❑ Meningismus (less common than in meningitis)

❑ Unilateral sensorimotor dysfunction (postinfectious encephalomyelitis [PIE]

Findings of **HSV** infection

- **Herpetic skin lesions**
- **Keratoconjunctivitis**
- **Oropharyngeal involvement**
- **Encephalitis symptoms**
- **Dissimenated HSE**

Work up

- bacterial, fungal, and autoimmune disorders can produce encephalitis, but most cases are **viral** in origin.
- Accordingly , studies may be performed to identify the **infectious agent** causing the encephalitis.
- It is important, when possible, to distinguish acute **arboviral encephalitides** from potentially treatable acute **viral encephalitides**, especially (HSE) and VZE as a high suspicion for these disorders and prompt treatment can reduce the severity of neurological sequelae and can be *lifesaving*

Investigations

- CBC
- KFT & LFT
- Electrolytes
- LP
- Serum glucose
- Coagulation profile

➢ A (LP) should be performed on all patients suspected of having a viral encephalitis.

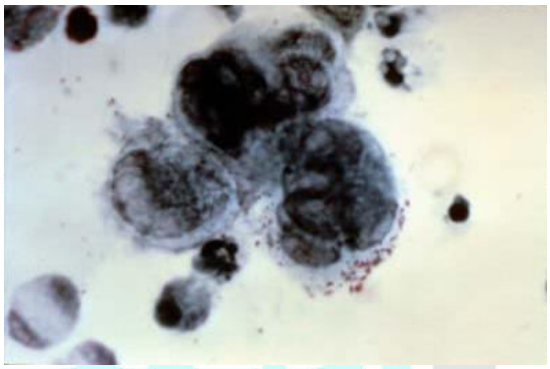
➢ A platelet count and coagulation profile are indicated in patients who have liver disease, and those in whom (DIC) is suspected. The patient may require platelets or fresh frozen plasma (FFP) before LP

For Specific Viruses:

a. HSV: Tzanck smear, Serology, Viral cultures, PCR

b. Arbovirus: Complement fixation antibodies

c. EBV: Heterophile antibody & cold agglutinin testing



CSF Analysis:

1. Perform Lumbar puncture if there is no papilledema or radiologic evidence for increased ICP .

- Opening pressure is usually elevetd.
- Pleocytosis is lymphatic if viral and usually neutrophilic if bacterial.
- Protein will be increased .
- Glucose will be variably decreased or occasionally Normal .
- RBC may be present esp. in HSV .

2. CSF cultures & Microscopy (G stain , acid fast Bacillus)

3. PCR for HSV, Entero and West Nile Viruses

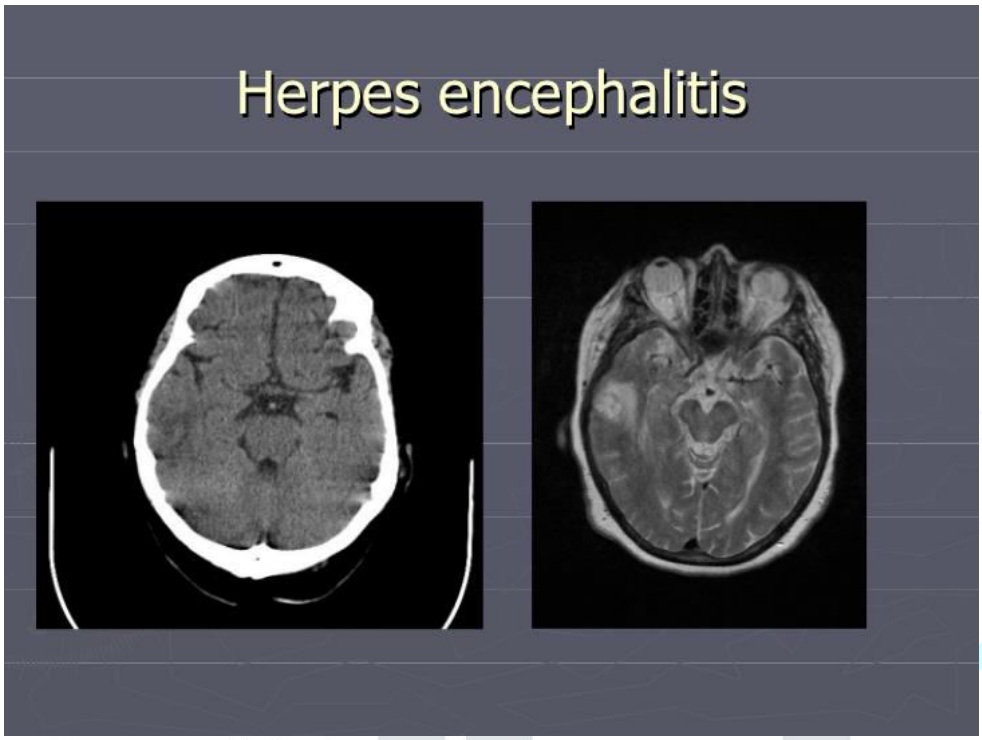
Imaging:

❑ Head CT , with and without contrast agent in virtually all patients with encephalitis before LP to search for evidence of elevated intracranial pressure (ICP), obstructive hydrocephalus, or mass effect before LP.

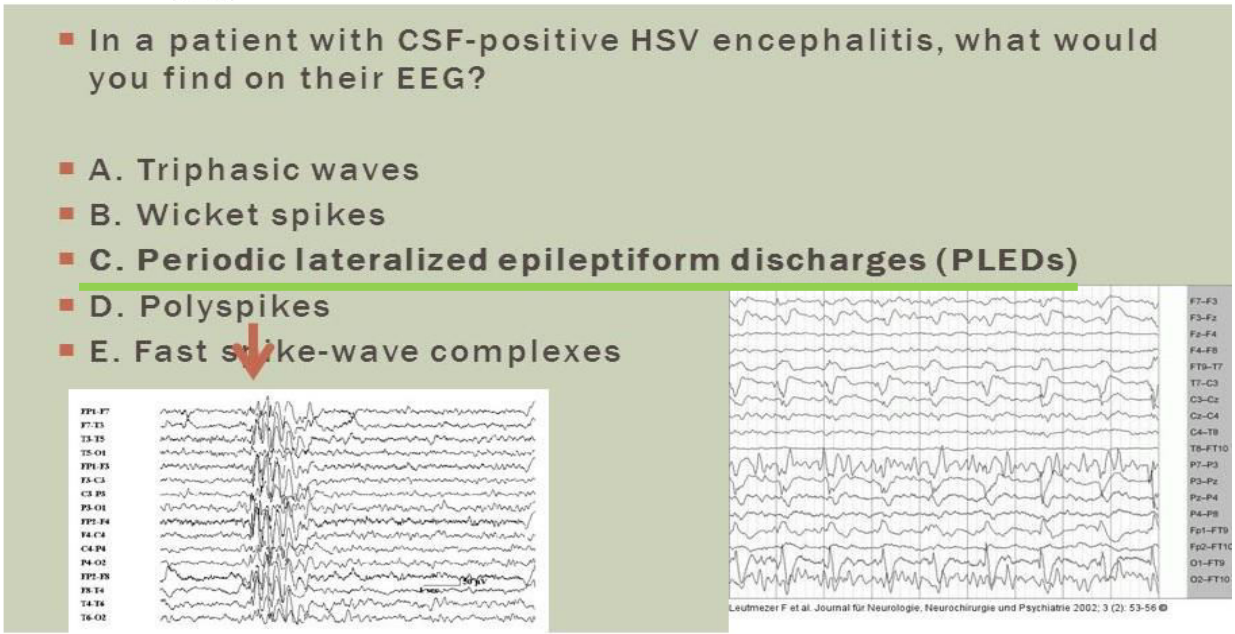
Differentiating encephalitis and meningitis || ↓

	Normal	Viral meningitis	Viral encephalitis	Bacterial meningitis
CSF findings				
Opening pressure	10 to 20 cm	Normal/high	Normal/high	High
Colour	Clear	Clear	Clear	Cloudy
White cells/mm^3	<5	5-1000	5-1000	100-50000
Differential	Lymphocytes	Lymphocytes	Lymphocytes	Neutrophils
CSF:plasma glucose	66%	Normal	Normal	Low (<50%)
Protein (g/L)	<0.45	Mildly raised (0.5 to 1)	Mildly raised (0.5 to 1)	Raised (>1)
Common causative agent		Enteroviruses, HSV-2, VZV	HSV-1	*Neisseria meningitidis, Streptococcus pneumoniae*
Clinical presentation		Headache, photophobia, neck stiffness, fever.	Fever, disorientation, speech disturbances, behavioural changes and seizures.	Headache, photophobia, neck stiffness, fever.
Outcome		Neuropsychological deficits e.g. cognitive dysfunction, sleep disorders, attention problems. Recurrences.	Death, memory impairment, behavioural change, dysphasia and epilepsy.	Death, hearing loss, disability, neuropsychological deficit

- Typical changes in encephalitis include paranchymal, meningeal and focal or diffuse enhancement of the brain (HSV medial Temporal lobe) .
- In toxoplasmosis, contrast-enhanced head CT typically reveals several nodular or ring-enhancing lesions because lesions may be missed without contrast.
- MRI should be performed in patients for whom use of contrast material is contraindicated.



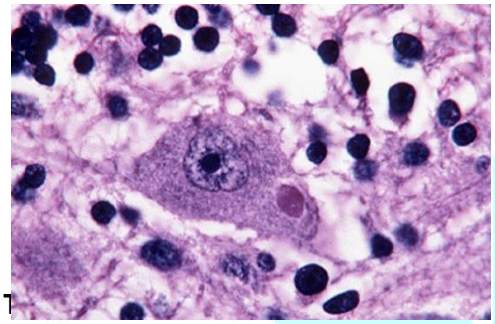
- (EEG) In HSE, often documents characteristic paroxysmal lateral epileptiform discharges (PLEDs), even before neuroradiography changes. Eventually, PLEDs are positive in 80% of cases; however, the presence of PLEDs is not pathognomonic for HSE.

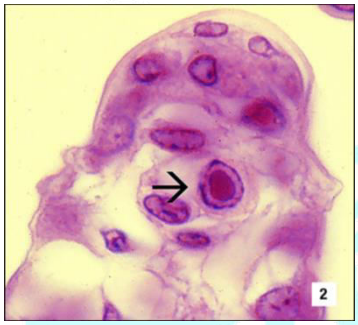


- ❑ The most important diagnostic test in the (ED) to rule out bacterial meningitis is prompt **Gram staining** and, if available, **(PCR)** of the CSF in patients with suspected HSV encephalitis.
- ❑ **PCR** for HSV DNA is 100% specific and 75-98% sensitive within the first 25-45 hours. Types 1 and 2 cross-react, but no cross-reactivity with other herpes viruses occurs
- ❑ Arguably, a series of quantitative PCRs documenting the decline of viral load with acyclovir treatment is strongly supportive of the diagnosis of HSV, and selected patients my avoid need for brain biopsy.

Brain Biopsy

- Although most histologic features are nonspecific, brain biopsy is the criterion standard because of its 96% sensitivity and 100% specificity.
- The presence of Negri bodies in the hippocampus and cerebellum are pathognomonic of rabies,
- As are HSV Cowdry type A inclusions with hemorrhagic necrosis in the temporal and orbitofrontal lobes.





- With the exception of HSV and HIV, there is no specific therapy for viral encephalitis.
- Management is supportive and frequently requires ICU admission, which allows aggressive therapy for seizures, timely detection of electrolyte abnormalities & when necessary, airway monitoring , protection & reduction of increased intracranial pressure .

HSV: i.v acyclovir (10-20 mg/kg/dose q8hr) for 14-21 days

HIV: combination of anti retroviral agent (zidovudin , didanosine)

ADEM: high dose of i.v corticosteroid

Subacute Sclerosing PanEncephalitis (SSPE)

"Dawson encephalites"

- Is a chronic progressive encephalitis caused by persistent **measles** virus infection of the CNS.
- Childrens with SSPE genrerally have a history of typical measles (mild or severe) with full recovery several years before the onset of neurological disease.
- The pathogenesis is that viral genes that encode envelop proteins like M protein have restricted expression so these protiens not produced so the virus stay in glial cells and neurons without provoke immunity then infection leads to SSPE
- Incidence : 0.06 cases per 1 million

Clinical presentation

- Asymptomatic period between the infection and the onset of SSPE (12 y)
- gradual, progressive psychoneurological deterioration consisting of :
  - seizure
  - myoclonus
  - ataxia
  - photosensitivity
  - *ocular abnormalities*
  - *spasticity*
  - *deterioration of schoolwork*
  - *Dementia and coma.*

- **PROGRESSION is RAPID**

1st stage……. Abnormal behavior, mental deterioration, intellectual difficulty THEN myoclonic jerks

2nd stage…….intensity of jerks and mental deterioration increase, reach to loss of ability to walk and speech impairment

Advance final stage…….decline in body function, blindness, mute or comatose patient

The total duration of illness may be short as few month, but most pt survive for three year at diagnosis.

DIAGNOSIS

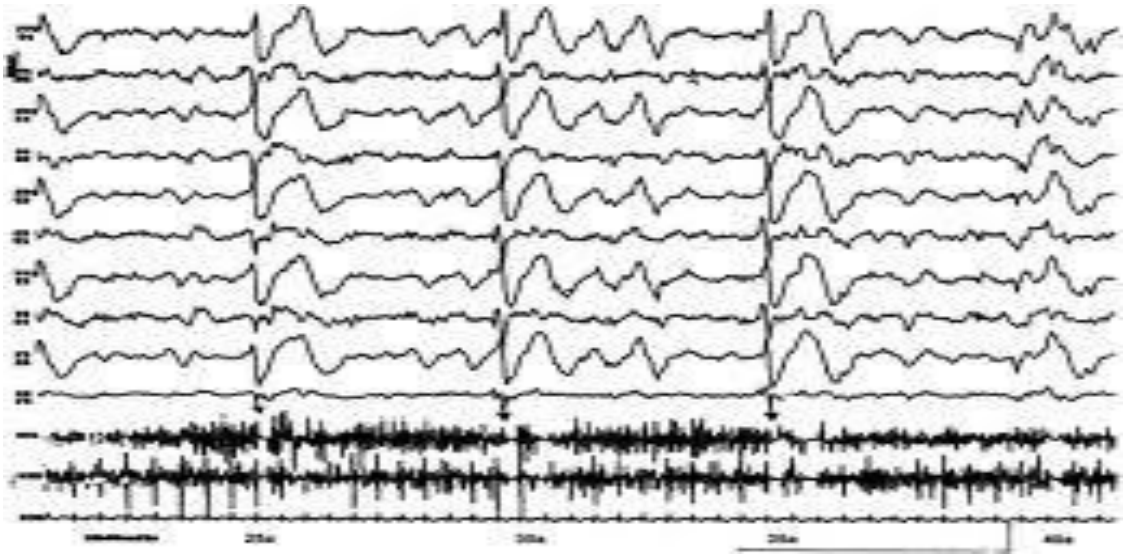
- Signs and symptoms
- Typical changes in EEG
- Elevated anti measles ab IgG in serum and CSF
- MRI - CT
- Typical histological finding in brain biopsy tissue no longer need.
- Pathologically, the white matter of both the hemispheres and brainstem are affected, as well as the cerebral cortex.
- **Eosinophilic inclusion** bodies are present in the nuclei of neurons and glial cells.

EEG

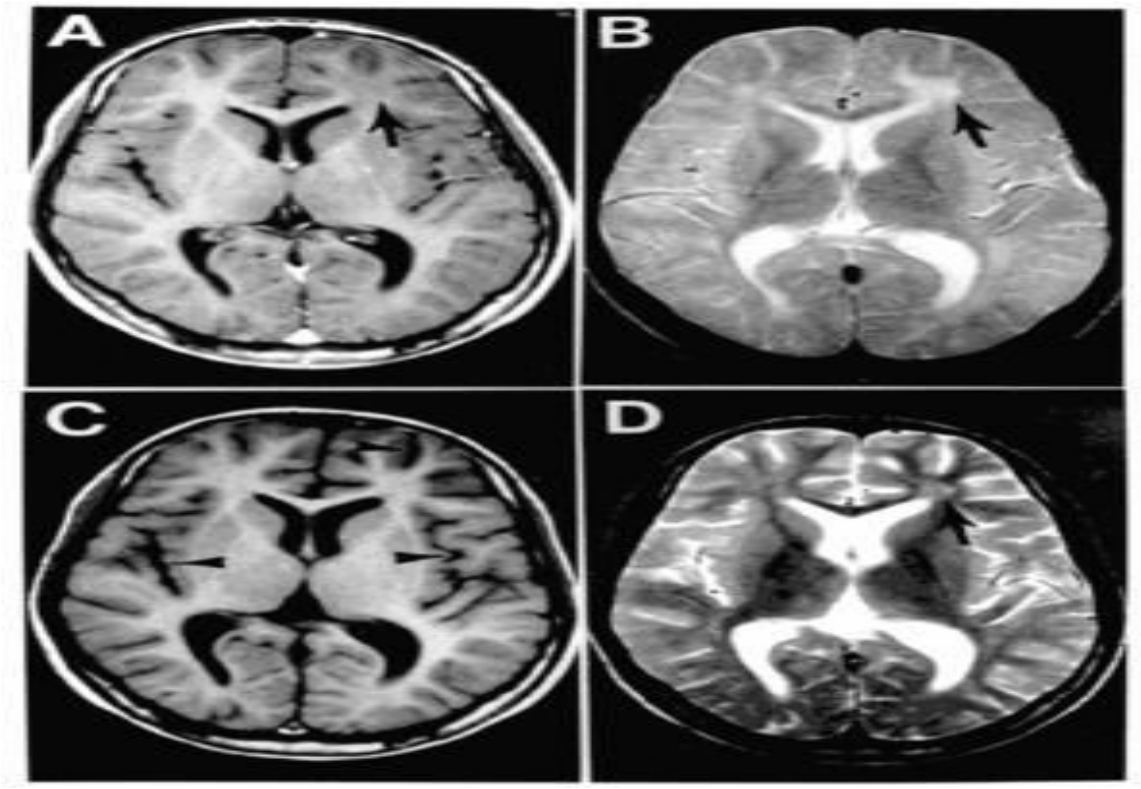
-Characteristic periodic slow wave complex (**Rademecker complex**)

-Moderate non specific slowing.

-Later may disorganized and show high amplitude random dysrhythmic slowing.



CT/MRI: variable cortical atrophy and ventricular enlargement or multifocal lesion in white matter.



Treatment:

combination of **inosine pranobex** 100 mg\kg\24hrs and **interferon** May prolong survival and may produce clinical improvement in degree of disability.

Prevention:

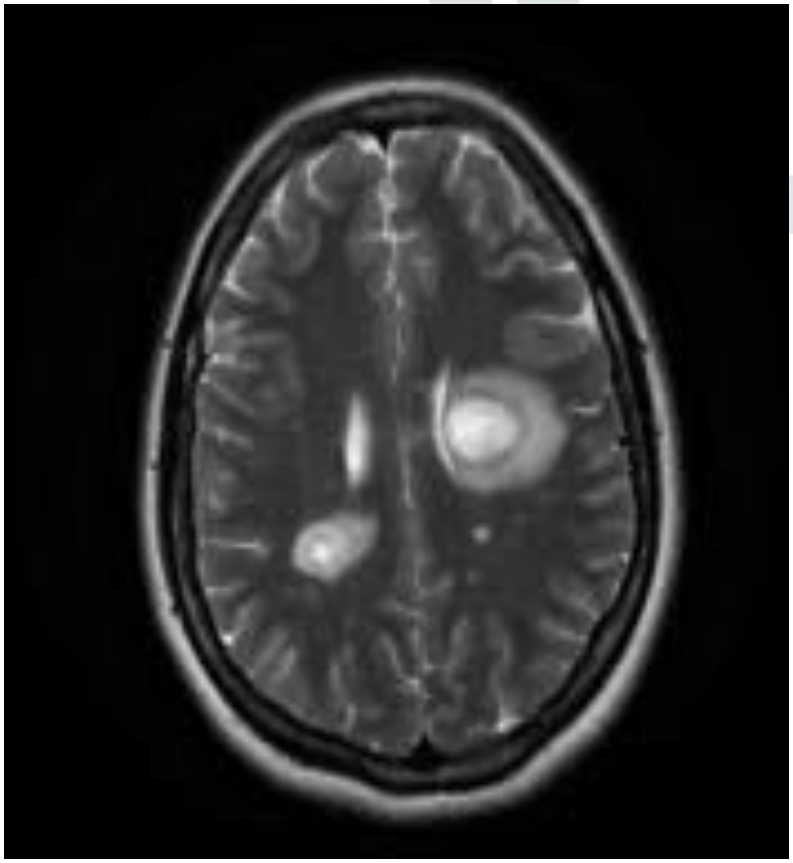
- **measles vaccination:** Death usually occurs within 3 years
- **Acute disseminated encephalomyelitis**
- **ADEM**
  - ADEM is a rare kind **monophasic**, **inflammatory**, **demylenating** disease that affect the entire CNS. Most often, children under age 10 will get it.

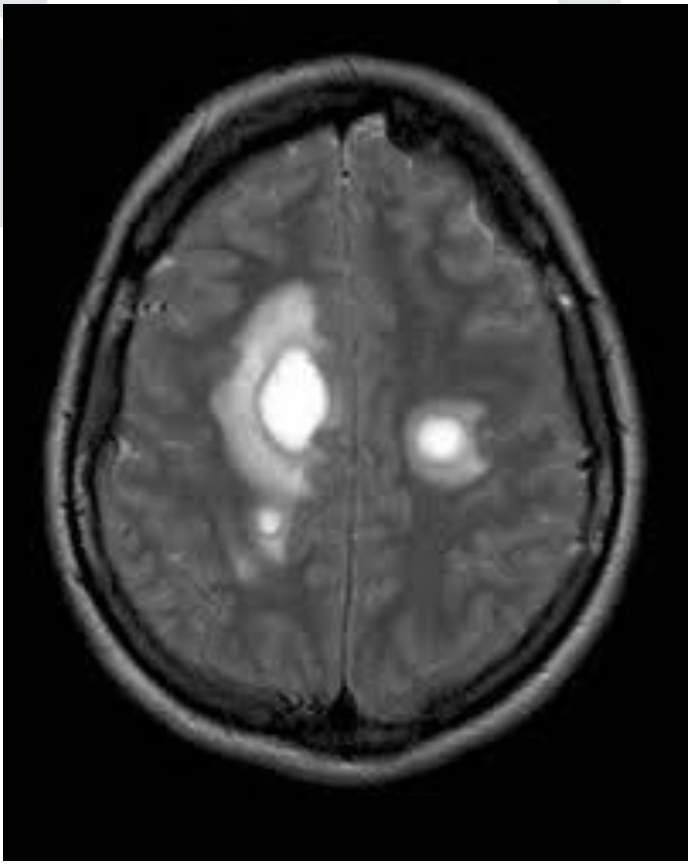
- ADEM seems to be an **autoimmune disease**.
- Experts don't know exactly what triggers it, but it could be an overreaction to an infection. Its usually occurs a week or two after infection (bacterial or viral)
- ADEM sometimes follows an immunization, particularly certain rabies shots and the vaccine for measles, mumps, and rubella. No direct connection has been made though.
- Other times, nothing out of the ordinary happens before symptoms appear.

Symptoms:

- Fever
- headache
- Sleepiness
- Behavior changes such as fussiness or confusion
- Nausea and vomiting
- seizure
- coma
- Diagnosis and Tests
- MRI
- Lumber puncture (marked polymorphonuclear pleocytosis , moderately elevated protein and normal glucose)

The condition has a lot in common with **multiple sclerosis** and other diseases that damage myelin. They share some symptoms, like muscle weakness, numbness, loss of vision, and loss of balance.





	ADEM	MS
AGE	<10 years	>10 years
Encephalopathy	Present	absent
Prognosis	Recovery is rapid and often complete	Recovery variable
ON	bilateral	unilateral
MRI lesion	Cortical and deep grey matter lesions (diffuse bilateral symmetrical lesion	Periventicular / callosal lesion (black holes)
CSF	lymphocytosis	Intrathecal IgG
Follow-up MRI	No new lesion	New lesion

Treatment:

- The goal is to get the inflammation down quickly and stop the immune system attack. This will likely take a week or two in the hospital.
- High doses of a powerful **IV corticosteroid** for a few days. They'll continue to take a steroid (as a pill or a liquid) for several weeks.
- **plasmapheresis**
- **IVIG**

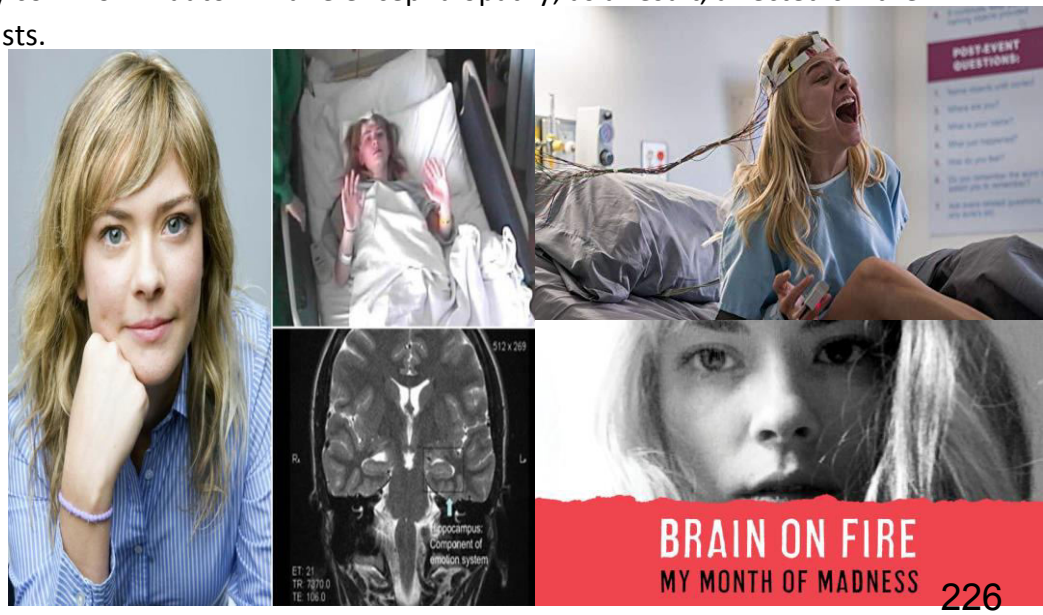
Pediatric Autoimmune Encephalitis (antibody mediated)

Autoimmune encephalitis is a diverse group of neuro-psychiatric disorders recognized recently **In 2007** .

The autoimmune process may be triggered by an infection, vaccine, or occult neoplasm

Neuropsychiatric symptoms are very common in autoimmune encephalopathy; as a result, affected children may be initially present to psychiatrists.

Susannah Cahalan:



- **Pathogenesis** is likely to be mediated by antibodies (Abs) to CNS proteins. The Abs are directed against membrane receptors and ion channel-associated proteins that are expressed on the surface of neurons in the CNS, Several antibodies have been demonstrated to be associated with paraneoplastic and nonparaneoplastic neurological syndromes divided into three groups:

(1) antibodies to intracellular antigens

(2) to cell-surface antigens

(3) to extracellular synaptic antigens

Autoimmune antibodies associated neurological syndromes:

1. **N-Methyl D-aspartate receptor** (NMDAR, NR1, NR2)
2. Voltage-gated potassium channel antibody syndromes
3. AMPAR (GluR1, GluR2) antibody syndrome
4. Glycine receptor antibody syndrome
5. Dopamine 2 receptor antibody syndrome (D2RA)
6. GABA receptor Ab syndrome
7. Metabotropic glutamate receptor antibody syndrome
8. IgLON5 Ab syndrome

- More than 90% of patients develop at least 3 of the following groups of symptoms within 1 month of disease onset: psychiatric features, memory disturbance, speech disorder, seizures, dyskinesias, decreased level of consciousness, autonomic instability, or hypoventilation.

- The most common presenting symptoms in children under the age of 12 years were abnormal behavior, seizures, and movement disorders.

- In pediatric ages, AE usually occurs in females, as in adults, less probable with a cancer association (more common in adults)

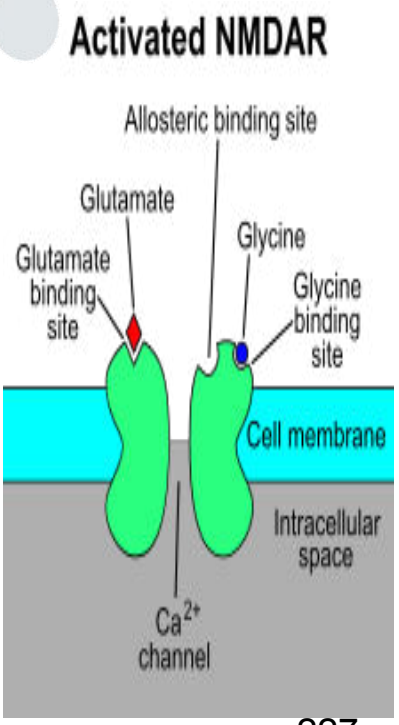
Anti-N-Methyl-D-aspartic acid encephalitis

- It is the most frequent and best characterized AE

- Herpes simplex virus encephalitis (HSVE) is an important trigger.

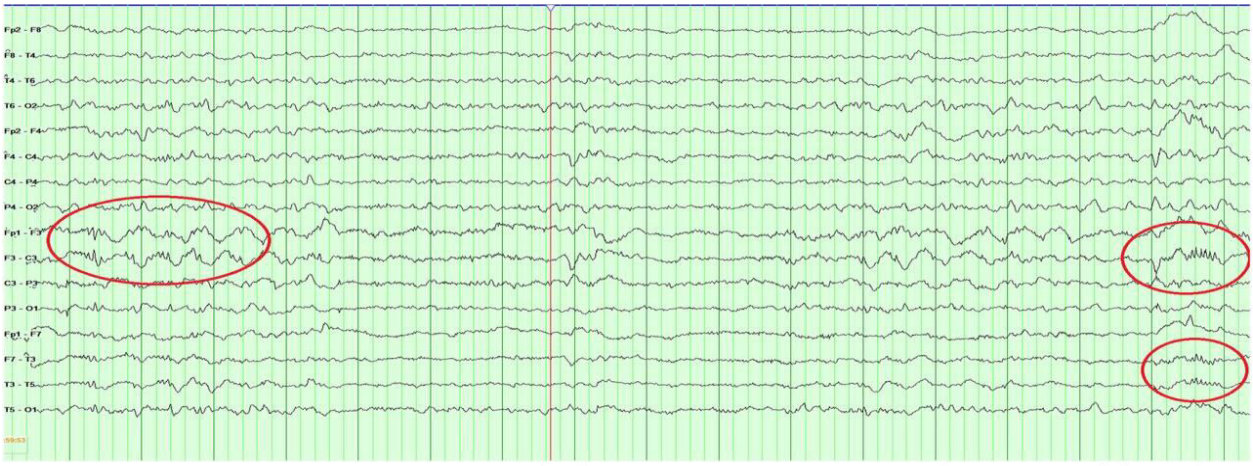
- Can be stimulated by an underlying tumor and the most frequently associated is ovarian teratoma.

- Autoantibodies of IgG subclass G1 bind the extracellular domain of the GluN1 subunits of the N-Methyl-D-aspartic acid receptor (NMDAR), with its internalization, resulting in the surface underexpression.



How to diagnose?

1. Electroencephalogram (EEG) is abnormal, showing focal or diffuse slowing or epileptiform discharges (extreme delta brush) has been described in AE and may support the diagnosis.



2. Brain (MRI): demonstrate cortical or subcortical, basal ganglia, and infratentorial T2 hyperintensities with or without transient meningeal enhancement.

3. Pathogenic anti-NMDAR autoantibodies: can be present both in serum and cerebrospinal fluid (CSF) = CSF more sensitive.

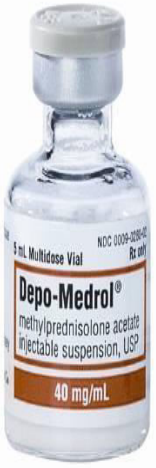
4. A paraneoplastic cause is much less probable in children so that testing for onconeural antibodies (e.g., Hu or Ma2) can be not strictly necessary at first instance.

5. Evaluation for malignancy should also ensue (chest and abdomen/pelvis imaging).

- Traumas, CNS infection, CNS vasculitis, CNS malignancies, toxic/drug ingestion, nonconvulsive status epilepticus, inborn errors of metabolism, and psychiatric conditions are differential diagnosis and must to be excluded while confirmatory autoantibody tests are being processed.

- In AE, CSF may be normal or abnormal, and in these cases, mild elevation of protein (<100 mg/dl) is the most common finding. A minority has a mild lymphocytic pleocytosis (<100 white blood cells/µL) or marked elevation of proteins

Acute treatment



1. high-dose corticosteroids (methylprednisolone 30 mg/kg/day, up to 1 g daily, for 3–5 days) then tapered using 1-2 mg/kg/day .

2. IV.Ig (2 g/kg divided over 2–5 days).

3. If no benefit is noticed, plasma exchange (PLEX), up to 3-5 times in 10 days .

- If there is no significant clinical improvement
- ** After 10 days with first-line therapies.

- Second-line therapy (rituximab and/or cyclophosphamide) should be started. Rituximab (375 mg/m^2 every week for 4 weeks) is usually well tolerated in children and so is preferred to cyclophosphamide.

Chronic treatment

❖ Chronic immunosuppression:

(e.g., mycophenolate mofetil, azathioprine) should be considered only in AE with a known risk for relapsing.

To date, no formal studies have assessed the duration of adequate immunosuppression.Thus, risks versus benefits must be analyze and discuss with patients and their families.

- **The prognosis is often Good in pediatric age, with 85% of full, but slow recovery (up to several months)**
- **Relapse in the remaining 15%.**

The Poisoned Pediatric Patient

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Education Gap

Poisonings remain a frequent source of morbidity and mortality in the pediatric age group. All pediatricians, whether in training or in practice, encounter these patients, yet toxicologic training is lacking in most pediatric residencies.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology of pediatric poisonings and explain how developmental milestones influence behavior that may lead to a poisoning exposure.
2. Perform a focused toxicologic physical examination and describe the various toxidromes.
3. Explain the primary acid-base disturbance in salicylate toxicity.
4. Determine which patient requires treatment after acute acetaminophen ingestion.
5. Provide the differential diagnosis of an anion gap metabolic acidosis.
6. Identify which drugs can lead to QRS and QTc prolongation and the treatment for each abnormality.
7. Describe the toxicologic differential diagnosis for hypoglycemia and explain the physiologic reasons why pediatric patients are at increased risk for complications.

AUTHOR DISCLOSURE Dr Toce has disclosed no financial relationships relevant to this article. Dr Burns has disclosed that she serves as a pediatric toxicology section editor for UpToDate® and a medical toxicology question writer for the American Board of Emergency Medicine and recently served on the Board of Directors for the American College of Medical Toxicology.

ABBREVIATIONS

AGMA	anion gap metabolic acidosis
ALT	alanine aminotransferase
APAP	acetaminophen
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
Cl^-	chloride
ECG	electrocardiogram
GI	gastrointestinal
GSH	glutathione
HCO_3^-	bicarbonate
IV	intravenous
K^+	potassium
NAC	N-acetylcysteine
NAPQI	N-acetyl-p-benzoquinoneimine
NPDS	National Poison Data System
PO	oral

INTRODUCTION

This review focuses on the epidemiology and initial evaluation and treatment of the poisoned pediatric patient. We emphasize the diagnosis and treatment of acetaminophen and aspirin toxicity, identifying and treating prolonged QRS/QTc, and developing a differential diagnosis for an anion gap metabolic acidosis (AGMA) and hypoglycemia (Table 1).

EPIDEMIOLOGY OF PEDIATRIC POISONING

Pediatric exposures and poisonings continue to be a significant cause of morbidity and mortality. According to the 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS), 1,326,789 toxic exposures occurred in children younger than age 20 years in 2014, representing

TABLE 1. **Introduction to the Poisoned Patient**

• Epidemiology of pediatric poisoning
• Toxicologic history, physical examination, and toxidromes
• Acetaminophen
• Aspirin
• Anion gap metabolic acidosis
• Electrocardiographic changes in the poisoned patient
• Toxic differential diagnosis of hypoglycemia

1,595 exposures per 100,000 population compared to 344 exposures per 100,000 population in adults. (1) In addition, 88 poisoning fatalities in children younger than age 20 years were reported, representing 7.5% of all fatalities reported to the NPDS in 2014. Pediatric poisonings occur across all ages, with children younger than age 3 years representing more than 33% of all exposures, and children age 5 years and younger representing slightly less than 50% of all exposures. Pediatric poisonings in children age 5 years and younger peaked in 2008 and are now decreasing (Fig 1). The reason for this decline is unclear, but some authors postulate that newer safety packaging and passive safety features (eg, single-dose packaging) are providing an added protective barrier.

Children are exposed to a variety of foreign substances, also known as xenobiotics. In children younger than age 6 years, exposures to household cleaning products and cosmetics represent the majority of calls to poison centers. Over-the-counter liquid acetaminophen and cold and cough medication are responsible for the most emergency department visits. Buprenorphine and clonidine account for the most hospitalizations. (2)

Developmental status plays an important role in pediatric poisonings. Because newborns do not have the mobility or the manual dexterity to manipulate child-resistant packaging, a poisoned neonate should raise suspicion for medical child abuse and/or neglect. As children become more mobile and are able to explore their surroundings, the risk for unintentional ingestion increases substantially. The increase in mobility coincides with the development of a pincer grasp and oral exploratory behavior, all of which lead to an increased risk for unintentional exposures. Primary care clinicians should use the 4- and 6-month health supervision visits as opportunities to discuss safe medication and household product storage as well as to review the process for calling the local poison control center, which can be reached toll-free in the United States at 1-800-222-1222.

Figure 1. Exposures involving children age 5 years and younger reported to the National Poison Data System (NPDS) by year. Such encounters peaked in 2008, a trend that mirrored total encounters reported to the NPDS. Data abstracted from the 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System: 32nd Annual Report (*Clin Toxicol.* 2015;53(10):962–1146).

As children become preteenagers and teenagers, experimentation with illicit drugs and intentional overdoses are more common. Parents need to balance adolescent autonomy, including the self-administration of medications, with the need for safety. The primary care clinician should use the yearly physical examination to obtain a full substance abuse history. Parents should be asked to leave the examination room and patients should be asked about illicit drug use, including the use of synthetic cannabinoids (eg, "K2," "Spice") and synthetic cathinones (eg, "bath salts"). These drugs are often sold legally in gas stations and head shops, and adolescents may mistakenly equate their availability with safety. Patients should also be asked about prescription drug abuse, both at home and within their peer group, and be screened for depression.

THE TOXICOLOGIC HISTORY, PHYSICAL EXAMINATION, AND TOXIDROMES

Several key pieces of information should be collected for every patient who has had a possible xenobiotic exposure. The specific xenobiotic, including dose, quantity, preparation (eg, liquid, pill, patch), and route (eg, ingestion, inhalation, dermal, ocular, intravenous [IV], rectal) of exposure should be assessed. Additional information regarding ingestion of an immediate- versus extended-release preparation is also important. Time of ingestion can guide the need for antidotal therapy. For example, the need for antidotal therapy for acetaminophen ingestion is based on a 4-hour serum acetaminophen concentration (see the Acetaminophen section in this article). Similarly, activated charcoal may be recommended if ingestion occurred within the previous 1 to 2 hours and the patient is able to swallow safely. If the exposure was unwitnessed or the patient is unresponsive, a comprehensive home medication list should be obtained.

A focused toxicologic physical examination should be performed on every poisoned patient. The toxicologic physical examination seeks to identify a group of signs and symptoms that are reliably caused by a specific xenobiotic. These groups of particular signs and symptoms are referred to as toxic syndromes or toxidromes. Identifying toxidromes allows a clinician to narrow the differential diagnosis to a subset of xenobiotics that correspond to the given toxidrome.

As with most patients, a careful review of the vital signs is paramount. The autonomic nervous system is frequently affected by xenobiotics, which can result in frequent vital sign abnormalities. The use of age-appropriate vital sign norms is imperative; a respiratory rate of 18 breaths/min may be normal in a teenager, but it is well below the 1st percentile in a 1-year-old child. Recognition of abnormal vital signs is particularly important in settings where ancillary staff is not accustomed to pediatric patients and treating clinicians might not be immediately cognizant of vital sign derangements. Fever in a poisoned patient could suggest excessive neuromuscular agitation from sympathomimetic or anticholinergic agents or may be the result of uncoupling of oxidative phosphorylation due to salicylate or dinitrophenol ingestion. On the other hand, hypothermia could indicate a sedative-hypnotic exposure, such as baclofen or a barbiturate. Tachycardia often signals excess sympathetic tone or anticholinergic activity, while the combination of bradycardia and hypotension has its own toxicologic differential diagnosis (Table 2). Tachypnea and hyperpnea could suggest respiratory compensation for a metabolic acidosis or may be due to direct medullary stimulation from a salicylate. Conversely, bradypnea points to an opioid overdose.

A thorough neurologic examination should be performed, including assessment of mental status, presence of miosis or mydriasis, accommodation, and nystagmus. Clonus and/or hyperreflexia should be tested for because these are signs of serotonergic excess and are often seen in selective serotonin reuptake inhibitor overdose. Examination of the oropharynx should focus on the presence or absence of moist mucous membranes and include investigation for any ulceration that

TABLE 2. **Toxicologic Differential Diagnosis for Bradycardia and Hypotension**

DRUG CLASS	EXAMPLES
Central α_2-adrenergic receptor agonists	Clonidine, guanfacine, dexmedetomidine, oxymetazoline, tetrahydrozoline
β-adrenergic receptor antagonists	Propranolol, metoprolol, esmolol
Calcium channel blockers	Diltiazem, verapamil, amlodipine
Cardiac glycosides	Digoxin, oleander (*Nerium oleander*), yellow oleander (*Thevetia peruviana*), foxglove (*Digitalis* species), lily of the valley (*Convallaria majalis*), red squill (*Urginea maritime)*
Acetylcholinesterase inhibitors	Organophosphates, carbamates, neostigmine, sarin, VX nerve gas

could suggest caustic ingestion. The respiratory evaluation should make note of excess secretions and/or wheeze, findings that may be present in organophosphate poisoning. Auscultation of the abdomen should be performed to assess for hypo- or hyperactive bowel sounds. Skin assessment should note the presence or absence of diaphoresis, flushing, or impaired peripheral perfusion.

Once vital signs have been assessed and a focused toxicologic examination has been performed, the treating physician should be able to ascertain if a patient fits into a defined toxidrome (Table 3). These characterizations help narrow the differential diagnosis and guide subsequent treatment. Unintentional ingestions by toddlers frequently involve a single substance, (3) which can increase the likelihood of identifying a toxidrome. As expected, polysubstance exposures can cloud the picture, and treating physicians must integrate multiple pieces of information to arrive at the correct diagnosis. Consultation with a medical toxicologist is advised for critically ill patients.

ACETAMINOPHEN

Epidemiology

Acetaminophen, or N-acetyl-para-aminophenol (APAP), remains one of the most commonly ingested xenobiotics, both intentionally and unintentionally. APAP is responsible for one-third of all pediatric emergency department visits for unsupervised over-the-counter liquid medication exposures in children younger than age 6 years. In addition, APAP is the cause of almost one-fifth of medication exposures involving oral over-the-counter solid medications, the highest single agent in each category. (3)

The reasons for such high exposure rates are varied. First, APAP is extremely prevalent in the community, with most homes having APAP in their medicine cabinets. Second, APAP is perceived as a safe medication by the lay public. (4) Third, multiple APAP-containing products are used to treat a variety of common maladies and families are often unaware that they are administering APAP. (5) Finally, dosing errors are common in APAP administration; parents frequently unknowingly administer supratherapeutic doses. (6)

Sources

As mentioned previously, a multitude of APAP-containing products are commonly prescribed. Oxycodone-APAP and hydrocodone-APAP combination products are frequently prescribed for the treatment of moderate-to-severe pain; over-the-counter cold and cough remedies commonly contain APAP in addition to dextromethorphan and chlorpheniramine or doxylamine; and APAP is used in combination with butalbital and caffeine to treat migraines. Families may be unaware that a medication contains APAP and administer concomitant doses, producing an unintentional toxic

TABLE 3. **Toxic Syndromes**

GROUP	VITAL SIGNS BP	P	R	T	MENTAL STATUS	PUPIL SIZE	PERISTALSIS	DIAPHORESIS	OTHER
Anticholinergics	-/↑	↑	±	↑	Delirium	↑	↓	↓	Dry mucous membranes, flush, urinary retention
Cholinergics	±	±	-/↑	-	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative-hypnotics	↓	↓	↓	-/↓	Depressed, agitated	±	↓	-	Hyporeflexia, ataxia
Opioids	↓	↓	↓	↓	Depressed	↓	↓	-	Hyporeflexia
Sympathomimetics	↑	↑	↑	↑	Agitated	↑	-/↑	↑	Tremor, seizure
Withdrawal from ethanol or sedative-hypnotics	↑	↑	↑	↑	Agitated, disoriented	↑	↑	↑	Tremor, seizure
Withdrawal from opioids	↑	↑	-	-	Normal, anxious	↑	↑	↑	Vomiting, rhinorrhea, piloerection, diarrhea, yawning

↑=increased, ↓=decreased, ±=variable, −=change unlikely, BP=blood pressure, P=pulse, R=respirations, T=temperature.

concentration. It is useful to remember that medication names ending in "-cet" always contain APAP (eg, Percocet, Roxicet, Fioricet).

Metabolism/Pharmacokinetics/Toxicokinetics/Pathophysiology

Orally administered APAP is rapidly absorbed from the gastrointestinal (GI) tract, with complete absorption occurring within 4 hours, although coingestion with anticholinergic drugs such as diphenhydramine or opioids can delay absorption. The metabolism of APAP is depicted in Fig 2. Of greatest concern to the treating clinician is generation of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). In therapeutic dosing, the body has sufficient stores of glutathione (GSH) to reduce and detoxify NAPQI. In overdose, alternative metabolic pathways become saturated, and there is increased formation of NAPQI, leading to depletion of GSH and accumulation of NAPQI.

As NAPQI accumulates, it binds to various cellular proteins, inducing hepatocellular death and liver inflammation. Toxicity manifests as rising aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values. In addition, depletion of GSH leaves the body susceptible to endogenous reactive oxygen species, leading to further damage. Histologically, damage is most profound in hepatic zone III due to the high concentration of the enzyme CYP2E1.

Clinical Effects

The stages of APAP toxicity are listed in Table 4. Clinicians must have a high index of suspicion due to the absence of specific signs and symptoms early in intoxication. Often patients present without symptoms or with vague abdominal pain, nausea, and emesis. As the toxic metabolite NAPQI accumulates, evidence of liver injury, namely, elevation of AST and ALT serum concentrations and prolongation of prothrombin time/International Normalized Ratio, develop. Of note, the accumulation of NAPQI takes time; APAP must be metabolized first, followed by depletion of the patient's supply of GSH. If a patient presents within 4 hours of ingestion and is already exhibiting signs of hepatocellular injury, the time of ingestion must be re-examined. Finally, every patient may not necessarily progress to the next stage of toxicity.

Diagnosis and Management

As previously mentioned, APAP ingestions are common in the pediatric population. As such, we recommend routine assessment of serum APAP concentration in all unknown ingestions and instances of self-harm. When the time of ingestion is known, we recommend obtaining a serum

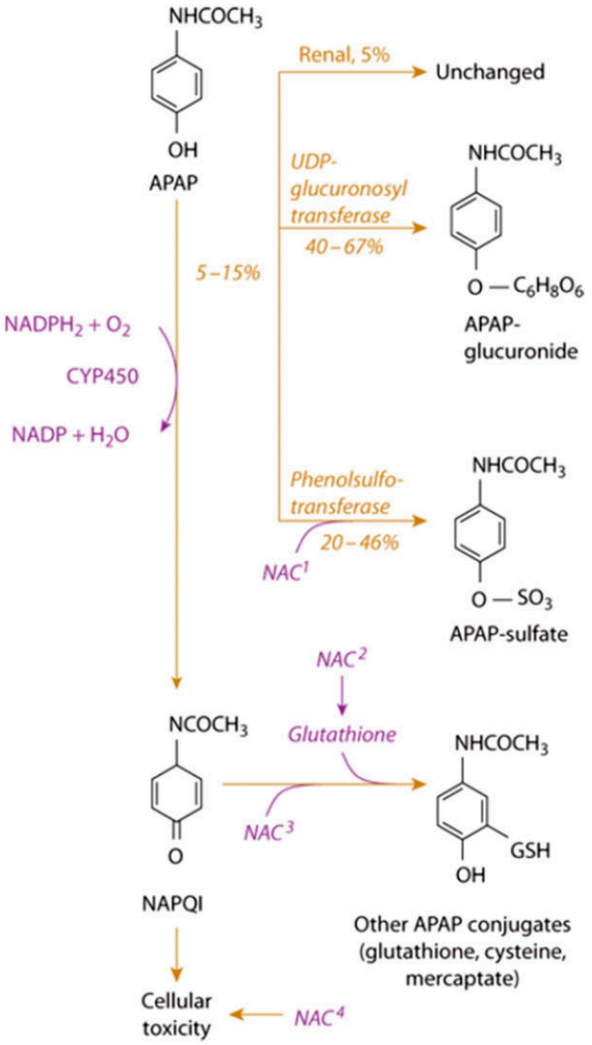

Figure 2. Important routes of acetaminophen (APAP) or N-acetyl-para-aminophenol metabolism in humans and mechanisms of N-acetylcysteine (NAC) hepatoprotection. NAC1 augments sulfation, NAC2 is a glutathione (GSH) precursor, NAC3 is a GSH substitute, and NAC4 improves multiorgan function during hepatic failure and possibly limits the extent of hepatocyte injury. Reproduced with permission from *Goldfrank's Toxicologic Emergencies*, 10th Edition, Copyright © 2015 by McGraw-Hill Education. Full text may be available from the McGraw-Hill Education website: www.mhprofessional.com.

APAP concentration at 4 hours after ingestion or later; by this time, absorption from the GI tract is complete and the need for antidotal therapy can be determined. Treatment with N-acetylcysteine (NAC) should be initiated if the patient's APAP concentration is above the treatment line on the Rumack-Matthew nomogram (Fig 3). Interestingly, the original treatment line, depicted by the dotted line in Fig 3, began at 200 μg/mL, but the Food and Drug Administration (FDA) required a 25% reduction for safety reasons. Thus, the current treatment line begins at 150 μg/mL. We recommend against empirical treatment with NAC within the first 8 hours of ingestion because research has shown no

TABLE 4. **Clinical Stages of Acetaminophen Toxicity***

STAGE	SIGNS/SYMPTOMS	LABS	TIME FRAME
I	Nausea Vomiting Malaise Pallor	Normal AST/ALT, INR	0-24 hours
II	Hepatotoxicity Right upper quadrant tenderness	Rising AST/ALT INR normal/elevated	12-72 hours
III	Fulminant hepatic failure Encephalopathy Coma	AST/ALT >10,000 U/L (167 μkat/L) INR elevated Elevated Cr Acidosis Lactemia	72-96 hours
IV	Recovery	Normalization of AST/ALT, INR	> 96 hours

**As acetaminophen is metabolized to the hepatotoxic metabolite N-acetyl-p-benzoquinoneimine, transaminases rise and focal tenderness develops. As hepatic injury worsens and the synthetic capability of the liver is impaired, prothrombin time/INR increase. Eventually, multisystem organ failure develops, after which patients recover, receive liver transplant, or die.*
ALT=alanine aminotransferase, AST=aspartate aminotransferase, Cr=creatinine, INR=International Normalized Ratio.

change in morbidity when treatment is initiated within 8 hours. (7) Therefore, it is reasonable to delay NAC therapy if the ingestion occurred within the last 8 hours, the patient is a reliable historian, and a serum APAP concentration can be obtained to determine the need for antidotal therapy. It is important to note that use of the Rumack-Matthew nomogram requires a single, one-time ingestion with a known ingestion time. Coingestion with drugs that alter GI absorption (eg, anticholinergics, opioids) can alter the pharmacokinetics of APAP absorption, necessitating additional assessments of serum APAP concentrations.

NAC is used to protect the liver and body from the oxidative stress of NAPQI and functions by detoxifying NAPQI, regenerating GSH, and scavenging for reactive oxygen species. It is available in IV and oral (PO) formulations. The decision to treat enterally versus parenterally is complex. Both formulations have been shown to be effective in treating APAP toxicity. The IV formulation is associated with a non-immunoglobulin E-mediated anaphylactoid reaction. Patients are at greatest risk early in treatment, typically during the loading dose, when the dose and concentration of NAC is the greatest. Nausea and vomiting are common with the PO formulation, raising the possibility of delayed treatment. The clinician must consider these issues with each patient.

Treatment of patients who do not "rule-in" for use of the Rumack-Matthew nomogram is difficult. There is general consensus that a patient who presents with a detectable APAP concentration and elevated transaminases in the setting of an unknown time of ingestion warrants treatment with NAC, and a patient with an undetectable APAP concentration and normal transaminase values does not. Management of the patient with detectable APAP and normal transaminases or undetectable APAP and elevated transaminases is less clear. Consultation with a medical toxicologist is recommended;

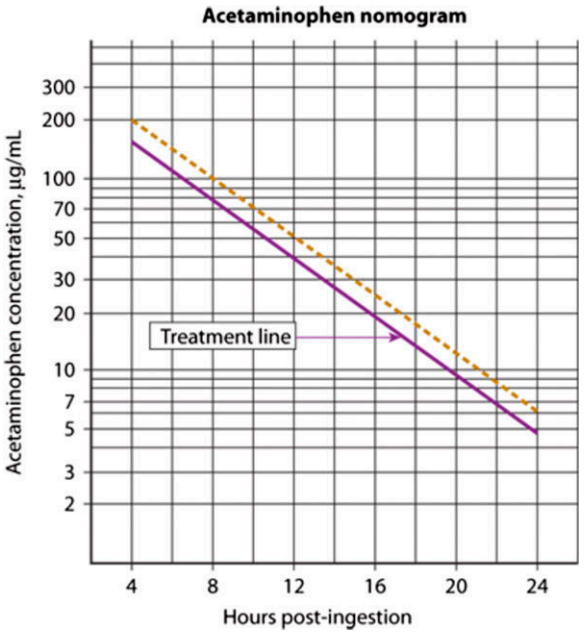

Figure 3. Rumack-Matthew nomogram (reconstructed) for determining the risk of acetaminophen-induced hepatoxicity after a single acute ingestion. Serum concentrations above the treatment line on the nomogram indicate the need for N-acetylcysteine therapy. Reproduced with permission from *Goldfrank's Toxicologic Emergencies*, 10th Edition, Copyright © 2015 by McGraw-Hill Education. Full text may be available from the McGraw-Hill Education website: www.mhprofessional.com.

following trends in serum APAP concentrations is key to appropriate management.

The most widely used treatment protocols involve a 21-hour course of IV NAC or a 72-hour course of PO NAC. Before discontinuing NAC, laboratory studies should be obtained, and treatment should continue until APAP is undetectable, hepatic transaminases are improving, serum prognostic markers (creatinine, prothrombin time/International Normalized Ratio, lactate, pH) are improving, and the patient is asymptomatic with no abdominal pain. (8)

ASPIRIN

Epidemiology

Aspirin, or acetylsalicylic acid (ASA), is a commonly used medication for both its analgesic and anti-inflammatory effects. It is used frequently today in the pediatric population to treat Kawasaki disease and in adult patients to mitigate the risks of myocardial infarction, colon cancer, and transient ischemic attacks. The most recent NPDS annual report states that exposures to aspirin as the sole agent in children age 19 years and younger occurred in 5,917 reported patients in 2014, with 3,459 of them occurring in children younger than age 6 years. Although aspirin was a significant cause of childhood poisonings several decades ago, the known association with Reye syndrome, coupled with the increased use of acetaminophen and nonsteroidal anti-inflammatory medications such as ibuprofen, have decreased the number of exposures reported annually to Poison Control Centers.

Sources

Aspirin can be found in various preparations, including chewable tablets and enteric-coated pills; its derivative 5-aminosalicylic acid is included in the medications sulfasalazine and mesalamine to reduce the inflammation in Crohn disease. Besides these single-ingredient medications, it can be found in combination with bismuth subsalicylate as an antidiarrheal treatment, magnesium subsalicylate in combination with caffeine as a weight loss agent, and as methyl salicylate (oil of wintergreen) as a flavoring agent or topical therapy for musculoskeletal pain. Of note, one teaspoon (5 mL) of oil of wintergreen contains approximately 7 g of salicylates, and pediatric fatalities with this amount have been reported. (9)

Metabolism/Pharmacokinetics/Toxicokinetics/Pathophysiology

Salicylates are well absorbed from the GI tract, particularly in the acidic milieu of the stomach. Absorption continues in the small intestine, with large overdoses of enteric products having the propensity to form bezoars. Acute ingestions of 150 to 200 mg/kg produce mild symptoms; amounts in the range of 300 to 500 mg/kg are considered serious. Salicylates cause toxicity by stimulating the respiratory center in the medulla that prompts an increase in respiratory rate and subsequent respiratory alkalosis; increased insensible fluid losses are also seen. Uncoupling of oxidative phosphorylation interrupts both glucose and fatty acid metabolism, with subsequent metabolic acidosis, hyperthermia, and hypoglycemia. Salicylates are metabolized in the liver and eliminated by the kidneys.

Clinical Effects

Pediatric aspirin ingestions are typically acute as compared to ingestions in adults, who may have drug accumulation following chronic use. Vomiting is the initial symptom and is due not only to irritation of the GI mucosa but also to stimulation of the chemoreceptor trigger zone in the medulla. Tinnitus (subjective sensation of ringing in the ears), tachypnea, and hyperpnea are also seen. Tachycardia can result from insensible fluid losses. With more severe intoxications, mental status changes become prominent, including delirium, agitation, and seizures due to cerebral edema. Hypoxia and chest radiograph changes consistent with pulmonary edema are another sign of critical poisoning.

Diagnosis and Management

Salicylate poisoning is typically diagnosed by history and/or laboratory evaluation. Even in the setting of an unknown overdose, physical examination findings suggestive of salicylism include vomiting, tachypnea, hyperpnea, tinnitus, and mental status changes; laboratory abnormalities can include a mixed respiratory alkalosis and metabolic acidosis on blood gas analysis. Serum aspirin concentrations of 30 mg/dL and higher require treatment with urinary alkalinization. Levels higher than 90 to 100 mg/dL after an acute poisoning are considered life-threatening, and concentrations greater than 60 mg/dL in patients chronically taking aspirin are regarded as serious; both require treatment with hemodialysis. The mnemonic "30-60-90" may facilitate remembering these laboratory values, but clinicians must ensure that the laboratory results are expressed in units of mg/dL to use the mnemonic. Aspirin concentrations should be measured every 1 to 2 hours until a peak serum concentration is reached and then carefully followed until the values decrease to less than 30 mg/dL. Serious problems can occur when values are not obtained for several hours and a precipitous rise in the serum salicylate concentration occurs due to bezoar rupture and/or erratic drug absorption. Decontamination with activated charcoal is paramount,

especially in the setting of enteric-coated products and/or massive overdoses that may form a bezoar. Urinary alkalinization with sodium bicarbonate therapy and hemodialysis are the mainstays of salicylate overdose management in conjunction with good supportive care. By raising the urine pH to 7.5 and greater, less unionized drug is available in the renal tubule for resorption, and subsequent urinary drug elimination is enhanced. The serum pH must be monitored simultaneously to ensure that it does not exceed 7.55. Hemodialysis is recommended in the following settings: acute serum salicylate concentrations of 90 mg/dL and greater; chronic serum salicylate concentrations of 60 mg/dL and greater; and in all instances of pulmonary or cerebral edema, renal insufficiency, seizures, unremitting acidosis, or acute clinical deterioration despite aggressive supportive care regardless of serum salicylate concentration. (10)

ANION GAP METABOLIC ACIDOSIS

Assessing a patient's acid-base status is essential when evaluating a critically ill patient or when an underlying cause of a patient's condition is unknown. This assessment is accomplished by measuring the patient's serum pH, bicarbonate (HCO_3^-), and partial pressure of carbon dioxide. With these 3 parameters, a clinician can classify the patient as having an acidosis or alkalosis and determine whether it is metabolic or respiratory. Due to its usefulness in identifying various poisonings, this review focuses on AGMA.

The concept of the anion gap is predicated on the concept of electroneutrality, which states that the number of negatively charged ions in a solution, in this case the serum, must equal the number of positively charged ions. In a practical sense, this means that the amount of sodium and potassium (the primary cations in serum) equals the amount of bicarbonate and chloride (the primary anions in the serum). An anion gap arises in the presence of unaccounted anions in the serum. Toxic alcohol ingestion can illustrate this concept further. Ingestion of ethylene glycol leads to AGMA due to accumulation of organic acids (glycolate and oxalate) that result from metabolism of ethylene glycol via alcohol dehydrogenase and then aldehyde dehydrogenase. As the buffering capability of bicarbonate is depleted, the measured HCO_3^- decreases. Replacing the HCO_3^- and, thus, maintaining electroneutrality are the unmeasured glycolate and oxalate anions, with the net result of an increased anion gap. Due to the decrease in HCO_3^-, this becomes evident as metabolic acidosis.

The anion gap is calculated by the following formula:

$$\text{Anion gap} = ([Na^+]) - \left([HCO_3^-] + [Cl^-]\right)$$

Of note, potassium (K^+) is omitted from the formula because K^+ rarely fluctuates more than 1 to 2 mEq/L above or below normal values, thus only minimally contributing to the anion gap. The definition of a "normal anion gap" varies with laboratory instrumentation; newer analyzers have the ability to detect higher chloride Cl^- concentrations, thus lowering the "normal anion gap." A baseline anion gap exists and is considered normal because sodium (Na^+) represents a larger proportion of the total extracellular cations compared to the contributions of HCO_3^- and Cl^- to the total extracellular concentration of anions.

The differential diagnosis of a high AGMA is represented by the acronym "MUDPILES" (Table 5). Although the underlying principles of why an anion gap develops are the same for all of the listed xenobiotics, how each achieves an anion gap varies. Some xenobiotics induce an AGMA via the generation of exogenous acids through their normal metabolism (eg, methanol, ethylene glycol, propylene glycol). Others function to poison the mitochondria and inhibit oxidative phosphorylation (eg, carbon monoxide, cyanide, hydrogen sulfide), leading to anaerobic metabolism and acid generation. Treatment varies according to the ingestion. Patients with methanol or ethylene glycol ingestion should have the first step in alcohol metabolism, alcohol dehydrogenase, blocked with fomepizole to inhibit the formation of toxic metabolites. Patients with salicylate concentrations greater than 30 mg/dL should have urinary alkalinization with sodium bicarbonate to enhance the elimination of salicylate ions. No matter what the exposure, patients with an AGMA require close monitoring and serial laboratory monitoring. It is important to remember that such patients often develop tachypnea and hyperpnea as they attempt to "blow-off" carbon dioxide to compensate for the metabolic acidosis. If a patient decompensates and requires intubation, care must be taken to match the patient's minute ventilation (minute ventilation = respiratory rate × tidal volume) before intubation; using a "normal" respiratory rate effectively hypoventilates the patient, leading to a harmful respiratory acidosis.

ELECTROCARDIOGRAPHIC CHANGES IN THE POISONED PATIENT

The electrocardiogram (ECG) is an integral tool in the diagnosis and management of the poisoned patient. It is a low-cost bedside diagnostic evaluation that can provide valuable, real-time information on the cardiac conduction system,

TABLE 5. **Toxicologic Differential Diagnosis for Anion Gap Metabolic Acidosis**

M	Methanol, metformin
U	Uremia
D	Diabetic ketoacidosis, alcoholic ketoacidosis
P	Paraldehyde, paracetamol (massive), propylene glycol, phenformin
I	Iron, isoniazid, ibuprofen (massive)
L	Lactate (including cellular asphyxiants [carbon monoxide, cyanide, hydrogen sulfide, sodium azide])
E	Ethylene glycol
S	Salicylates

identifying dysrhythmias, heart block, conduction abnormalities, and myocardial ischemia. We recommend that an ECG be obtained on all patients who present with an unknown ingestion and in instances of self-harm. Hundreds of xenobiotics alter the normal flux of ions through various myocardial channels, which form the basis for normal cardiac function (Fig 4), with antiepileptics, antipsychotics, antidepressants, local anesthetics, and antiarrhythmics frequently causing ECG abnormalities. Two specific intervals deserve special consideration: the QRS complex and the QT interval.

The QRS Complex

In the most basic sense, the QRS complex represents ventricular depolarization. Ventricular depolarization results from the influx of sodium into the myocardial cell through voltage-sensitive sodium channels during phase 0. These channels are susceptible to blockade by a myriad of xenobiotics (Table 6), with the net effect of sodium-channel blockade being prolongation of the QRS complex. Interestingly, most xenobiotics preferentially block the right-sided conduction pathway, producing an incomplete right bundle branch block that is detected on ECG. In addition to QRS prolongation, sodium-channel blockade can manifest in an elevation in the terminal R-wave in lead aV_R, with previous research suggesting that an R-wave greater than 3 mm is predictive of seizure or dysrhythmia in patients who have tricyclic antidepressant poisoning. (11)

In the poisoned patient, we consider a QRS greater than 100 msec to be abnormal, and such a prolongation warrants treatment with antidotal therapy. (12)(13) Previous research on patients poisoned with tricyclic antidepressants showed that those who had a QRS less than 100 msec had no instances of seizure or ventricular dysrhythmias, but a QRS greater than 100 msec was associated with an ~30% chance of seizure and a QRS greater than 160 msec was associated with a 50% chance of ventricular dysrhythmia. (14) In patients with known cardiac conduction delays, the treating clinician must weigh the risks and benefits of treatment. Because most pediatric patients have healthy conduction systems, a QRS greater than 100 msec warrants treatment unless the patient has a known cardiac conduction abnormality, such as a right bundle branch block.

Treatment of a widened QRS complex is aimed at reversing the inhibition of ventricular depolarization. As mentioned previously, ventricular depolarization is a sodium-dependent process, and xenobiotics (eg, tricyclic antidepressants, local anesthetics, class 1a and 1c antiarrhythmics) that affect the QRS primarily do so through blockade of fast-sodium channels. To overcome this blockade, IV sodium bicarbonate is administered to increase the extracellular concentration of sodium and disrupt the sodium-channel blockade. The effect of sodium bicarbonate therapy is twofold. First, by increasing the extracellular concentration of sodium, the number of sodium ions that may enter the myocardial cell through unblocked channels is increased, thus promoting depolarization. Second, by making the blood more alkaline, the amount

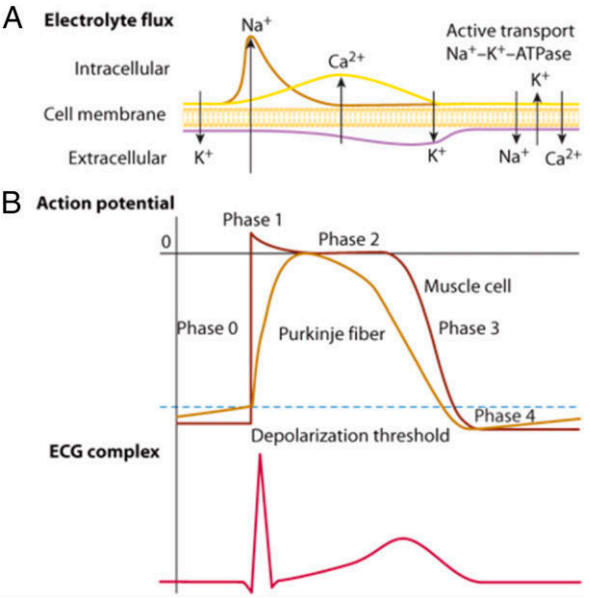

Figure 4. Relationship of electrolyte movement across the cell membrane (A) to the action potential and the surface electrocardiographic (ECG) recording (B) over a single cardiac cycle. Ca=calcium, K=potassium, Na=sodium. Reproduced with permission from *Goldfrank's Toxicologic Emergencies*, 10th Edition, Copyright © 2015 by McGraw-Hill Education. Full text may be available from the McGraw-Hill Education website: www.mhprofessional.com.

TABLE 6. **Xenobiotics Associated with QRS and QTc Prolongation on Electrocardiography***

QRS WIDENING AGENTS	QTc PROLONGING AGENTS
Bupivacaine	Antipsychotics
Bupropion	Class Ia, Ic, and III antiarrhythmics
Carbamazepine	Fluoroquinolones
Class Ia and Ic antiarrhythmics	Macrolides
Cocaine	Methadone
Diphenhydramine	Ondansetron
Lamotrigine	Selective serotonin and norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine)
Quinidine	Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline, citalopram)
Tricyclic antidepressants	

**Agents that prolong the QRS block fast-acting sodium channels and delay phase 0 of the myocardial action potential and ventricular depolarization. Drugs that prolong the QTc inhibit phase 2 or 3, often through I_{Kr} blockade.*

of uncharged xenobiotic, which has a lower affinity for sodium channels, is increased, thus decreasing channel blockade. (15)(16)

In pediatric patients, we recommend a bolus of 1 to 2 mEq/kg of sodium bicarbonate followed by a continuous infusion of 150 mEq of sodium bicarbonate in 1 L of 5% dextrose to infuse at 1.5 to 2 times the maintenance IV fluid rate. It is important to closely monitor the patient's QRS complex and the serum pH and potassium because bicarbonate administration causes progressive alkalemia as well as hypokalemia as potassium is shifted intracellularly and excreted by the kidneys. Bicarbonate therapy should be continued until the QRS is less than 100 msec or has returned to the patient's baseline. Continuing to monitor the patient's QRS after the bicarbonate infusion has been discontinued is critical because patients are at risk for rewidening the QRS after discontinuation of therapy.

QTc Interval

The QT interval is measured from the onset of the QRS complex to the end of the T-wave and encompasses ventricular depolarization, onset, and completion of repolarization. The QT increases with bradycardia and shortens with tachycardia. As such, various formulas have been used to adjust for rate variation, with the Bazett formula being one of the most common to calculate the QT corrected for heart rate (QTc):

$$QTc(msec) = QT(msec)/\sqrt{RR\ interval(sec)}$$

Many drugs induce QTc prolongation through potassium channel blockade, specifically by blocking the HERG-encoded subunit of the delayed rectifier potassium channel (I_{Kr}) (Table 6). This leads to prolongation of the repolarization (phase 3) portion of the cardiac action potential. In addition, alterations in serum electrolytes, primarily calcium, magnesium, and potassium, can alter the QTc. Finally, xenobiotics that affect the fast-sodium channel prolong the QRS and, thus, can cause QTc prolongation.

The result of a prolonged QTc interval is an increased chance of early afterdepolarizations, which are spontaneous depolarizations of myocardial tissue before repolarization is complete. If depolarization is large enough, premature ventricular contractions can occur, with the possibility of progressing to ventricular tachycardia, ventricular fibrillation, or torsade de pointes.

Treatment of a prolonged QTc includes electrolyte supplementation, including potassium, magnesium, and calcium. A goal serum magnesium concentration of 2 mEq/L and an ionized calcium of 2 mmol/L is recommended. If a patient progresses to torsade de pointes, magnesium sulfate should be infused, and if the patient is hemodynamically unstable, electrical defibrillation is required. It is also critically important to stop all nonessential QTc-prolonging agents. Many common drugs, such as ondansetron, antipsychotics, antidepressants, and a variety of antibiotics, can prolong the QTc and place the patient at further risk for ventricular dysrhythmia. For the purposes of simplicity, we define a potentially dangerous prolonged QTc interval as a QTc greater than 500 msec, with the understanding that age-specific normal values exist.

TOXICOLOGIC DIFFERENTIAL DIAGNOSIS OF HYPOGLYCEMIA

The definition of hypoglycemia in the pediatric patient continues to be controversial. As valuable as it would be to have a serum glucose concentration that identifies hypoglycemia in every patient, the fact remains that individuals differ in their response to glucose concentrations. One patient may be symptomatic at a serum glucose concentration of 60 mg/dL (3.33 mmol/L) and another may not. As such, the definition of hypoglycemia should be a serum

glucose concentration that induces a hypoglycemic or counterregulatory response and/or inhibits normal brain function.

The first component of the counterregulatory response is a decrease in insulin secretion, which occurs when blood glucose concentrations fall below 80 to 85 mg/dL (4.44-4.72 mmol/L). Further decreases in blood glucose concentrations cause an increase in glucagon secretion, which commonly appears at a blood glucose concentration of less than 70 mg/dL (3.89 mmol/L). Glucagon acts on the liver to promote glycogenolysis and gluconeogenesis. Next, autonomic stimulation, manifested by rising epinephrine concentrations, occurs, which produces many of the clinical symptoms of hypoglycemia (Table 7). Of note, adrenergic receptor antagonists (eg, β-adrenergic receptor antagonists such as propranolol) can blunt this response. Finally, cortisol concentrations rise to promote hepatic gluconeogenesis.

The pediatric patient is at increased risk of hypoglycemia due to a child's higher baseline rate of glucose utilization and relatively limited supply of gluconeogenic precursors, most notably alanine, due to lower muscle mass reserve. In infants, hypoglycemia is often due to inborn errors of metabolism and congenital hyperinsulinism. As patients become mobile, the risk of xenobiotic-induced hypoglycemia increases.

TABLE 7. **Clinical Manifestations of Hypoglycemia***

NEUROGENIC SYMPTOMS DUE TO AUTONOMIC NERVOUS SYSTEM STIMULATION	NEUROGLYCOPENIC SYMPTOMS DUE TO LOW CEREBRAL BLOOD GLUCOSE
• Tachycardia	• Headache
• Diaphoresis	• Visual changes
• Nausea/vomiting	• Confusion
• Pallor	• Somnolence
• Hypothermia	• Coma
• Weakness	• Seizure

**Autonomic symptoms are the result of elevated epinephrine concentrations in response to hypoglycemia; central nervous system changes occur in response to a decrease in the amount of available cerebral blood glucose, the brain's preferred energy source. Patients who are exposed to a β-adrenergic receptor antagonist and become hypoglycemic may not exhibit the symptoms of autonomic stimulation due to adrenergic blockade but should have expected neurologic changes.*

The toxicologic differential diagnosis for hypoglycemia is displayed in Table 8 and can be remembered by the acronym "HOBBIES." Ethanol is a common acquired cause of hypoglycemia in the pediatric patient and should be on the differential diagnosis list for any child who presents to the emergency department with ataxia, acute change in mental status, and hypoglycemia. Via ethanol's metabolism by alcohol dehydrogenase, nicotinamide adenine dinucleotide is depleted, inhibiting the oxidation of lactate to pyruvate. Pyruvate is a key step in gluconeogenesis, and depletion can lead to fasting hypoglycemia in the pediatric patient.

Sulfonylurea exposure can be potentially life-threatening in the pediatric population due to its ability to produce profound hypoglycemia. Any patient with potential exposure to sulfonylureas, such as glyburide and glipizide, should be admitted for overnight monitoring and frequent blood glucose evaluations for several reasons. The overnight period is a physiologic period of fasting during which blood glucose hemostasis is dependent on gluconeogenesis and glycogenolysis. In addition, cortisol concentrations are at their lowest point overnight.

Sulfonylureas and meglitinides induce hypoglycemia via the release of endogenous insulin from the pancreatic β-cell. Treatment involves administration of dextrose-containing fluids to immediately correct hypoglycemia as well as octreotide to suppress further insulin secretion. Octreotide is a semisynthetic somatostatin analog that inhibits pancreatic β-cell insulin release. Research has shown that prompt administration of octreotide to hypoglycemic patients exposed to sulfonylureas leads to fewer dextrose boluses and fewer episodes of hypoglycemia. (17)

Finally, β-adrenergic receptor antagonists induce hypoglycemia through their inhibition of gluconeogenesis and glycogenolysis, both of which are adrenergic-mediated processes. As mentioned previously, many of the clinical

TABLE 8. **Toxicologic Differential Diagnosis for Hypoglycemia**

H	Hypoglycemics, oral (eg, sulfonylureas, meglitinides)
O	Other (eg, unripened fruit from the Ackee [*Blighia sapida*] tree, litchi fruit, intravenous quinine)
BB	β-adrenergic receptor antagonists ("β-blockers")
I	Insulin
E	Ethanol
S	Salicylates

manifestations of hypoglycemia are adrenergically mediated and as such, are absent in a patient who has β-adrenergic receptor antagonist-induced hypoglycemia.

Summary

- Pediatric poisonings are common, representing more than 60% of all calls reported to the National Poison Data System in 2014.
- A 4-hour or later serum acetaminophen (APAP) concentration should be obtained on all patients who present after intentional ingestion. On the basis of evidence from research as well as expert consensus (level C), we recommend against empirical treatment with N-acetylcysteine if the APAP ingestion occurred within the previous 8 hours. (7)
- QRS prolongation is due to fast-sodium channel blockade and results in delayed ventricular depolarization. On the basis of some research evidence as well as consensus (level C), if the QRS is greater than 100 msec, a trial of sodium bicarbonate is warranted. (12)(13)(14)
- Sulfonylureas can cause life-threatening hypoglycemia. Pediatric patients are at increased risk for hypoglycemia, especially overnight. Treatment is with dextrose-containing fluids and octreotide (level C).
- The local poison center can be reached toll-free in the United States at 1-800-222-1222.

References and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/38/5/207.

PIR Quiz

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1. You are preparing for a number of well-child visits for the day in your outpatient clinic. The first patient that you see is a 2-week-old male coming for nursery follow-up evaluation. This is the firstborn child of a young mother who is concerned about him getting into household products. In thinking about the necessary anticipatory guidance messages regarding poisoning prevention, which well-child visits are ideal opportunities to discuss safe medication, household product storage, and how to reach the poison control center?
    A. First and second newborn visits.
    B. Four- and 6-month well-child visits.
    C. One- and 2-year well-child visits.
    D. Preteen and teenage well-child visits.
    E. Six- and 7-year well-child visits.
2. You are in the emergency department caring for a teenage girl with acetaminophen (APAP) ingestion. The patient went to her room last night upset because she broke up with her boyfriend. This morning, her mother came to her room to wake her up for school and found her asleep with an opened bottle of acetaminophen on the floor. There were multiple pills on the floor and on the bed and the bottle was empty. The parents do not recall how many pills were in the bottle before last night. They brought her to the emergency department. She is acting and feeling normal. You obtain serum studies. Which of the following findings and contexts would warrant initiation of treatment for APAP ingestion?
    A. APAP concentration of 30 μg/mL, elevated transaminases, and ingestion 9 hours ago.
    B. APAP concentration of 30 μg/mL, elevated transaminases, and ingestion time unknown.
    C. APAP concentration of 30 μg/mL, normal transaminases, and ingestion time 9 hours ago.
    D. APAP concentration undetectable, elevated transaminases, and ingestion 9 hours ago.
    E. APAP concentration undetectable, normal transaminases, and ingestion time unknown.
3. You are admitting a 2-year-old child who ingested an unknown quantity of homeopathic oil while at her aunt's house. Initial blood gas analysis shows a mixed respiratory alkalosis and metabolic acidosis. This suggests ingestion of which of the following xenobiotics?
    A. Acetylsalicylic acid.
    B. Clonidine.
    C. N-acetyl-para-aminophenol.
    D. Synthetic cannabinoids.
    E. Synthetic cathinones.
4. A 14-year-old boy is brought to the emergency department after being found unresponsive at home. An empty pill container was found next to him, with a label for a tricyclic antidepressant. Electrocardiography reveals a QRS of greater than 100 msec. Which of the following intravenous treatments is indicated?
    A. Fomepizole.
    B. Magnesium sulfate.
    C. N-acetylcysteine.
    D. Ondansetron.
    E. Sodium bicarbonate.

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5. You are caring for a 20-month-old child brought to the emergency department after he was found lethargic next to a viscous pool of an unknown substance. Initial laboratory findings show a blood glucose of 60 mg/dL (3.33 mmol/L). You discuss with the medical student working with you the causes of hypoglycemia in a child of this age. Which of the following factors places children of this age, who are mobile, at increased risk of hypoglycemia?

   A. Decreased risk of xenobiotic ingestion.
   B. Greater muscle mass reserve.
   C. Increased supply of gluconeogenic precursors.
   D. Limited alanine supplies.
   E. Lower baseline rate of glucose utilization.

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition

- Chapter 369: Poisoning - https://pediatriccare.solutions.aap.org/chapter.aspx?sectionid=125490789&bookid=1626

Point-of-Care Quick Reference

- Poisoning - https://pediatriccare.solutions.aap.org/Content.aspx?gbosid=165602

Parent Resources from the AAP at HealthyChildren.org

- Poison Prevention & Treatment Tips: https://www.healthychildren.org/English/news/Pages/Tips-for-Poison-Prevention-and-Treatment.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

Sickle Cell Disease

Timothy L. McCavit, MD*

Author Disclosure
Dr McCavit has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

In the United States, sickle cell trait is carried by 7% to 8% of people of African ancestry, and the sickle hemoglobinopathies are estimated to affect 90,000 to 100,000 people.

Objectives

After completing this article, readers should be able to:

1. **Understand how the sickle hemoglobin mutation leads to the various manifestations of sickle cell disease (SCD).**
2. **Identify common health maintenance needs for children with SCD.**
3. **Recognize the common acute complications of SCD and their treatment.**
4. **Assess the risks and benefits of the common treatment modalities for SCD.**
5. **Discuss the improved prognosis for children with SCD.**

Abbreviations

ACS:	acute chest syndrome
Hgb:	hemoglobin
HgbS:	sickle hemoglobin
HSCT:	hematopoietic stem cell transplantation
HU:	hydroxyurea
IPD:	invasive pneumococcal disease
PAH:	pulmonary artery hypertension
PCV13:	pneumococcal conjugate vaccine
PROPS:	Prophylactic Penicillin Study
RBC:	red blood cell
SCD:	sickle cell disease
SS:	sickle cell anemia
$S\beta^0$:	sickle β^0 thalassemia
TCD:	transcranial Doppler
TRJV:	tricuspid regurgitant jet velocity
VOC:	vaso-occlusive crises

Epidemiology

The World Health Organization estimates that 7% of the world's population carries a hemoglobin (Hgb) mutation and that 300,000 to 500,000 children are born each year with severe hemoglobinopathy. The sickle Hgb (HgbS) mutation occurred independently at least four times (three times in sub-Saharan Africa and once in India or the Arabian peninsula) in regions with endemic malaria. In the heterozygous state, the sickle mutation provides protection against infection by the *falciparum* species of malaria and likely confers a survival advantage, leading to its continued high prevalence in some populations of sub-Saharan Africa and the Middle East/India. In the United States, sickle cell trait is carried by 7% to 8% of people of African ancestry, and the sickle hemoglobinopathies are estimated to affect 90,000 to 100,000 people. (1) US newborn screening data suggest that 1 in 2,500 newborns is affected by a form of sickle cell disease (SCD).

Nomenclature

SCD refers to a group of heterogeneous disorders that are unified by the presence of at least one β globin gene affected by the sickle mutation (position 6, β-globin gene; codon GAG changes to codon GTG, coding for glutamic acid instead of valine). Homozygotes for the sickle mutation have sickle cell anemia (SS) or Hgb SS disease, which accounts for ~60% to 65% of SCD.

When inherited with the sickle mutation in a compound heterozygous state, other β-globin gene mutations lead to other distinct forms of SCD. The most common of these is HgbC, which, when coinherited with the sickle mutation, leads to sickle hemoglobin-C disease, accounting for 25% to 30% of all SCD. Coinheritance of a β thalassemia mutation with the sickle mutation leads to sickle β^0 thalassemia ($S\beta^0$) or sickle β^+ thalassemia, which account for 5% to 10% of all SCD (β^0 indicates no β globin production; β^+ indicates diminished β globin production).

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Other less common β-globin mutations that lead to SCD when coinherited with HgbS include Hgbs O^{Arab}, D, and E. When discussing patients with SCD, precise nomenclature is important because of the phenotypic variability between the various forms.

It should also be noted that the term "sickler" is viewed as a derogatory term by many in the SCD clinician and patient community and is inappropriate to use in communication among clinicians. More appropriate terminology would be "a patient with sickle cell disease."

Pathophysiology

The sickle mutation leads to the replacement of hydrophilic glutamic acid by a hydrophobic valine. The presence of the hydrophobic valine residue allows HgbS to polymerize in the deoxygenated state. In addition to low oxygen tension, low pH and an increased concentration of HgbS within the red blood cell (RBC) encourage polymer formation. HgbS polymerization ultimately causes RBCs to take on the characteristic sickle shape in a reversible fashion. Repeated episodes of polymerization and "sickling" can cause an RBC to be irreversibly sickled. In the circulation, these stiff, nondeformable sickled cells can lead to vaso-occlusion, with resultant tissue ischemia. As a result of or in addition to HgbS polymerization, other pathophysiologic mechanisms in patients with SCD have been observed, including activation of the vascular endothelium, leukocytosis, leukocyte activation, platelet activation, and oxidative stress from tissue reperfusion. Additionally, reduced RBC deformability and injury of the RBC cytoskeleton caused by the presence of HgbS polymers ultimately result in both intravascular and extravascular hemolysis. In the past 10 years, it has been suggested that nitric oxide depletion secondary to intravascular hemolysis may contribute to certain complications of SCD, such as pulmonary artery hypertension (PAH), although this postulate is controversial. (2)(3)

Diagnosis

Before newborn screening, the diagnosis of SCD was made only after a potentially devastating complication prompted medical attention. Justification of newborn screening for SCD was provided by the Prophylactic Penicillin Study (PROPS) in 1986 (see below), and since then, universal newborn screening with Hgb electrophoresis (Table 1) or other methods has become the standard in the United States. Certain states also provide confirmation of an SCD electrophoresis result by DNA sequencing. As with most genetic conditions, prenatal diagnosis of a fetus with SCD is possible in the first trimester through chorionic villus sampling or in the second trimester through amniocentesis.

Table 1. Newborn Screen Results for Common Hemoglobinopathies

Newborn Screening Result	Interpretation
F, A	Normal
F, A, S	Sickle cell trait
F, S	SS, $S\beta^0$, or S-HPFH
F, S, C	HgbS-C disease
F, S, A	Sickle β^+ thalassemia
F, A, S, Barts	Sickle cell trait with α thalassemia trait
F	β-thalassemia major

β thalassemia trait is not diagnosed in the newborn period with most current newborn screening techniques. A=HgbA; C=HgbC; F=fetal Hgb; S=HgbS; S-HPFH=sickle with hereditary persistence of fetal Hgb.

Health Maintenance

SCD is medically complex, affecting virtually any organ in the body, so children born with SCD benefit from well-coordinated, comprehensive, multidisciplinary care. This care occurs ideally through regular interactions with both a primary care provider and a pediatric hematologist. Psychologists, social workers, and expert nursing support play important roles as patients and families adjust to life with SCD and its complications. Additionally, other subspecialty expertise in SCD is important, including neurology, pulmonology, nephrology, radiology, ophthalmology, otorhinolaryngology, general surgery, and anesthesiology. In addition to the elements of routine health maintenance highlighted in Table 2, common chronic problems and activities discussed at routine visits include enuresis, sleep and sleep-disordered breathing, jaundice, mental health and adjustment to chronic disease, and sports participation. In the teenage years, fostering self-care, responsibility, and readiness for transition to adult care become the focus.

Clinical Presentation

Effects on Blood

A variety of hematologic abnormalities typify SCD. Anemia is the primary hematologic manifestation of SCD, with the severity determined by genotype (Table 3), in addition to the specific patient's rates of hemolysis, erythropoiesis, and plasma volume expansion. (4) After the transition to adult β globin expression occurs in the first

Table 2. **Health Maintenance Timeline for Children With SCD**

Intervention/Activity	Timing
Comprehensive medical evaluation (with a hematologist, where possible)	First visit by 2 mo of age 3–4 / y until age 5 1–2 / y after age 5
Genetic counseling	First visit, re-educate as needed
Pneumococcal prophylaxis	
Twice daily prophylactic penicillin	As soon as possible
PCV13 series	2, 4, 6, and 12–15 mo
Pneumococcal polysaccharide vaccine	First dose at 2 y of age
Haemophilus influenzae type b vaccine	2, 4, 6, and 12–15 mo
Meningococcal vaccine (MCV4)	1st dose at 24 months of age or older; 2 total doses at least 8 weeks apart
Influenza virus vaccine	First after 6 mo after birth, annually thereafter
Education on spleen palpation and signs/symptoms of splenic sequestration	First visit and every visit thereafter until age 3–5 y
TCD ultrasonography*	First screen at 2 y of age If normal, repeat annually until age 16 If conditional, repeat every 3–6 mo If abnormal ×2, initiate transfusions
Asthma screening	Screening history at 1 y of age, then annually PFTs at 6 y of age, then every 5 y†
Growth and maturation assessment	At least annually
Assessment of school performance	At least annually upon school entry
Assessment for sickle retinopathy by an ophthalmologist	Annually beginning at 10 y of age
Evaluate for sickle nephropathy by creatinine, urinalysis, urine protein/creatinine ratio or microalbuminuria‡	Annually beginning at 10 y of age‡
Counseling on transition to adult care‡	Annually beginning at 13–15 y of age‡
Screening performed at some centers	If done, ideal timing is unknown
History, physical or radiograph for avascular necrosis of femoral heads	
History and physical for obstructive sleep apnea	
Echocardiography for elevated TRJV	
MRI for silent stroke and cerebral vasculopathy	

PFT=pulmonary function test, TCD=transcranial Doppler.
*For patients with SS and $S\beta^0$.
†Disagreement among experts about the necessity of PFT screening.
‡Limited evidence base to support a specific method or timing.

year of life, children with SCD typically maintain stable baseline Hgb levels with significant fluctuations occurring usually during acute disease complications. Additionally, a leukocytosis with typical total white blood cell counts of 15,000 to 25,000/mm^3 is observed. A mild thrombocytosis is also common among patients with SCD, with average platelet counts of 400,000 to 475,000/mm^3.

Infection

PNEUMOCOCCUS AND PROPHYLACTIC PENICILLIN. A predilection to infection by the encapsulated organism *Streptococcus pneumoniae* has long been recognized in children with SCD, particularly those with SS, due to functional asplenia. Before attempts at prophylaxis, the incidence of invasive pneumococcal disease (IPD) was six episodes/100 patient years, with a peak in the first 3 years of life. Beginning in the late 1970s and early 1980s, the pneumococcal polysaccharide vaccine became standard for children with SCD. In 1986, the landmark PROPS clinical trial revealed an 84% decrease in the risk of IPD in children receiving daily prophylactic penicillin, compared with those receiving placebo. (5)

The PROPS II study attempted to answer the question of whether prophylactic penicillin could be discontinued safely at 5 years of age. (6) The number of IPD events was unexpectedly low during the study period, so a difference in the rates of IPD between groups could not be demonstrated clearly. This finding has led to a variable practice among sickle cell centers with some

Table 3. **Hematologic Parameters for the Common Forms of SCD**

Name	Genotype	Typical Baseline Values		
		Hgb, g/dL	Reticulocytes, %	MCV
Sickle cell anemia	SS	6–9	10–20	Normal*
Sickle hemoglobin-C disease	SC	9–11	3–10	Low normal to slightly low
Sickle β-zero thalassemia	$S\beta^0$	6–9	10–20	Low
Sickle β-plus thalassemia	$S\beta^+$	10–12	2–5	Low

MCV=mean corpuscular volume.
*Unless α thalassemia trait is coinherited with SS.

recommending daily penicillin for life (or at least until age 18 years), whereas others recommend cessation of prophylaxis at age 5 years. Similarly, the role of penicillin in patients with Hgb SC and other mild genotypes is controversial.

The heptavalent pneumococcal conjugate vaccine, licensed in 2000, has led to a further 70% decrease in the incidence of IPD, now estimated to be 0.3 to 0.5/100 patient years. (7) After heptavalent pneumococcal conjugate vaccine licensure, nonvaccine serotypes emerged as the most common cause of IPD, particularly serotype 19A. Pneumococcal conjugate vaccine (PCV13), licensed in 2010, includes 19A and other currently prevailing serotypes. Current standard practice should include daily prophylactic penicillin beginning before 2 months of age, the PCV13 series as recommended for all children, and at least two doses of pneumococcal polysaccharide vaccine, with the first dose at 2 years of age.

FEVER MANAGEMENT. Because of the risk of IPD, any fever (typically defined as ≥38.3°C) is treated as a medical emergency for children with SCD. Urgent evaluation of all febrile episodes, including physical examination, complete blood count, and blood culture, is of utmost importance. Although hospitalization for observation is sometimes necessary, patients with SCD evaluated for fever without a source who lack certain high risk features (white blood cell count >30,000/mm³ or <5,000/mm³, fever >40°C, "ill-appearing") may be managed safely as an outpatient after intravenous administration of an empiric, antipneumococcal antibiotic (eg, ceftriaxone). Other factors that must be considered in deciding whether to discharge a patient from the emergency department include the age of the patient, the ability of the family to return promptly for recurrent fever or clinical deterioration, and the availability of close follow-up.

APLASTIC CRISIS. Infection by parvovirus B19 leads to a maturation arrest for RBC precursors in the bone marrow for ~10 to 14 days. In hematologically normal children, this arrest in RBC production is not problematic because of the 120-day lifespan of normal RBCs. In SCD, however, the RBC lifespan is between 10 and 20 days, so cessation of RBC production for 10 to 14 days can lead to profound anemia. Signs and symptoms of profound anemia, including pallor, fatigue, decreased activity, altered mentation, and poor feeding, are typical of aplastic crises. Laboratory evaluation reveals severe anemia with reticulocytopenia and occasional thrombocytopenia. The management of an aplastic crisis includes transfusion support as needed until reticulocyte recovery has occurred. Family members of patients with SCD who are experiencing an aplastic crisis should be evaluated if they have SCD and no previous history of parvovirus infection.

Acute Pain

VASO-OCCLUSIVE CRISIS. Severe, episodic pain is the clinical hallmark of SCD. Commonly referred to as vaso-occlusive crises (VOC), these episodes can occur from infancy until old age, although they increase in frequency throughout childhood with a peak in the mid 20s. The pathophysiologic mechanism for most VOC is bone marrow ischemia with resultant infarction. Risk factors for more frequent VOC include severe genotype (SS or $S\beta^0$), increasing age, and high baseline Hgb level. On the other hand, a high baseline fetal Hgb concentration is protective. VOCs are triggered commonly by infection, emotional stress, or exposure to cold, wind, or high altitude. The episodes may occur in many locations throughout the body, although the lower back, legs, and arms are most common. Using the frequency of interactions with the health-care system as a proxy for pain frequency and severity may vastly underestimate the problem of pain in SCD. It is, therefore, crucial that health-care providers specifically assess pain occurring at home during routine visits.

The severity and duration of VOCs vary from minor pain lasting minutes to excruciating pain lasting days. Examination of a patient having a VOC may reveal erythema, edema, joint effusions, or point tenderness, but none of these signs may be present and they are not required for the diagnosis. A minor decrease in Hgb concentration from baseline and an increased white blood cell count are common but nonspecific laboratory features.

The approach to treating severe acute pain, sadly, has not changed in decades. Opioid analgesics, anti-inflammatory medications, and intravenous fluids remain the mainstays of treatment. RBC transfusions, however, do not aid in the resolution of severe VOCs. Recognition and treatment of psychosocial contributors to acute and chronic pain are other key elements to VOC management. Many pain crises can be treated at home with distraction and other coping behaviors in addition to oral pain medications. Prevention of VOCs can be aided by the avoidance of precipitating factors, the use of hydroxyurea (HU, see below), and maintenance of intravascular volume through oral fluid intake.

DACTYLITIS. Dactylitis is a specific type of VOC that occurs in infants and young children with SCD, especially SS. Dactylitis is defined by tender, erythematous, and edematous hands or feet (Fig 1). It occurs in 25% of infants by 1 year of age and 40% by 2 years of age, although significant variability in the prevalence has been noted among studies. Principles of dactylitis management do not differ from other VOCs; analgesics and intravenous fluids are key. Dactylitis before 1 year of age was identified as one of three prognostic factors used to predict severe outcome (frequent VOCs, frequent acute chest syndrome [ACS], acute stroke, or death) in a large cohort study of pediatric patients with SCD in the United States, although this finding could not be replicated in a large independent pediatric cohort study.

Pulmonary Complications

ACUTE CHEST SYNDROME. The very term ACS suggests an incomplete understanding of this phenomenon. Clinically, ACS is defined by a new pulmonary infiltrate (Fig 2) on chest radiograph in addition to one or more of the following: fever, tachypnea, dyspnea, hypoxia, and chest pain. ACS is a common and potentially lethal complication of SCD. The incidence of ACS is highest (25 episodes/100 patient years) in children between 2 and 5 years of age. When the underlying cause of ACS was investigated in detail including bronchoscopy, 45% of patients had no identifiable cause, whereas infection caused 30% of cases. The most common infectious causes of ACS included *Chlamydia pneumoniae* (28% of infections), viral infection (22%), and *Mycoplasma pneumoniae* (20%). Pulmonary infarction and fat embolism caused 16% and 8% of all ACS cases, respectively. The pathogenesis of ACS likely varies, depending on the cause, but commonly includes inflammation, pulmonary vascular occlusion, ventilation/perfusion mismatch, airway hyperreactivity, and pulmonary edema.

The treatment of ACS includes supplemental oxygen, empiric antibiotics (including a macrolide for coverage of atypical pathogens), bronchodilators, and careful management of analgesia and intravascular volume. Blood transfusion is another fundamental treatment for ACS. A decrease in Hgb level from baseline and an increasing

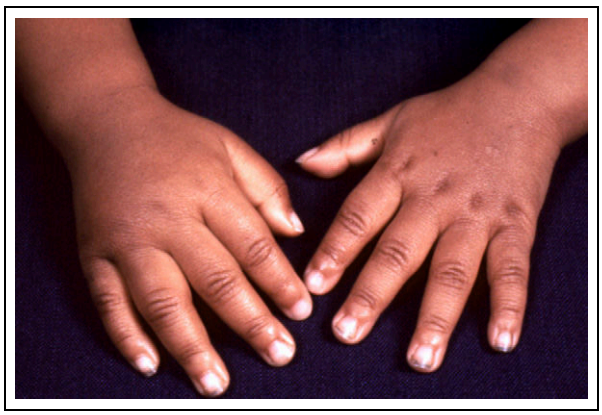

Figure 1. Dactylitis is characterized by tender, erythematous, and edematous hands or feet. Courtesy of Doernbecher Children's Hospital, Portland, Oregon.

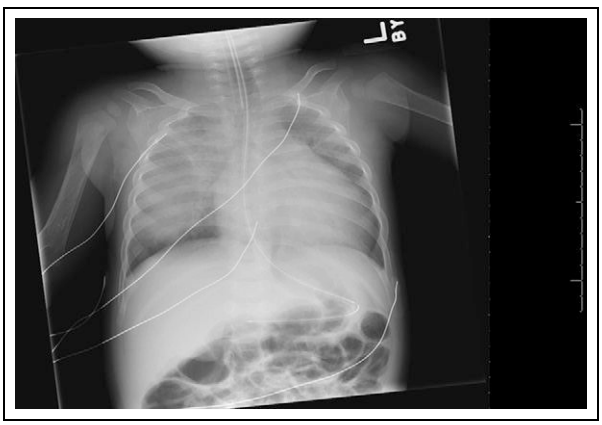

Figure 2. Chest radiograph of an 18-month-old infant with SS and severe ACS with diffuse bilateral infiltrates.

supplemental oxygen requirement are common indications for transfusion in ACS. Simple transfusion may be adequate for mild to moderate ACS, but exchange transfusion should be considered early in the course of progressive or severe ACS.

In addition to transfusion, supportive respiratory care, up to and including mechanical ventilation and extracorporeal membrane oxygenation, may be necessary in severe cases. Finally, corticosteroids have been shown to reduce the severity of ACS hospitalizations. Unfortunately, corticosteroid use is complicated by a high rate of "rebound" VOC, so if used at all, corticosteroids should be reserved for the most severe cases.

ASTHMA. Asthma is prevalent in children with SCD, as in the general population, affecting nearly 20% of patients. In SCD, a diagnosis of asthma is associated with higher rates of ACS, VOC, and early death. The mechanism by which asthma influences the severity of SCD is unclear but could relate to inflammation, ventilation-perfusion mismatching, or other mechanisms. Because of the strength of the SCD/asthma association, patients with SCD should be screened for asthma on an annual basis by history and physical examination beginning at 1 year of age. Additionally, some groups recommend screening with pulmonary function testing at least every 5 years, beginning at 6 years of age. Patients with SCD with persistent asthma also should be followed by a pulmonologist, regardless of severity.

PULMONARY ARTERY HYPERTENSION. PAH is a severe complication of SCD that typically occurs in adulthood. Its pathogenesis may relate to nitric oxide depletion secondary to release of free Hgb into the plasma from chronic intravascular hemolysis. Symptoms of PAH may include exertional dyspnea, fatigue, and syncopal events. Right heart catheterization classically has been required for the diagnosis of PAH, although an elevated tricuspid regurgitant jet velocity (TRJV) on echocardiography is correlated with catheter-determined pulmonary artery pressures. Thus, echocardiography for TRJV is used commonly as a screening test for PAH in adults with SCD, and, although controversial, has been suggested as a screening test for children with SCD as well. Abnormal TRJVs have become synonymous with PAH in some segments of the literature, but right heart catheterization is still recommended for a definitive diagnosis and before treatment of PAH.

Neurologic Manifestations

STROKE. Children with SS and Sβ^0 have long been recognized as being at risk for acute stroke. The risk of stroke is 10% in the first 20 years of life, with a peak incidence between 4 and 8 years of age. (8) Most strokes in SCD are ischemic in nature, with hemorrhagic stroke accounting for less than 10% of the total. The presenting symptoms of acute stroke in SCD include hemiparesis, facial droop, aphasia, and more generalized symptoms, including stupor and, rarely, seizure. Acute stroke symptoms may mimic a VOC in a young child reluctant to use a painful limb. The pathogenesis of acute stroke is incompletely understood but includes a vasculopathy marked by hypertrophy of the intima and media layers of the large arteries in the anterior cerebral circulation (primarily the middle cerebral arteries).

The evaluation of a patient suspected of experiencing acute stroke should include a careful history and neurologic examination; emergent radiographic evaluation by MRI or computed tomography followed by MRI when MRI is not immediately available; and a laboratory evaluation, including blood count, reticulocyte count, Hgb S percentage, and blood group and screen.

The principle underlying the treatment of acute stroke is the rapid reduction of the Hgb S percentage. This goal may be achieved through simple RBC transfusion or partial manual exchange, although automated exchange transfusion with erythrocytopheresis reduces the Hgb S percentage more efficiently and is widely regarded as standard practice. This treatment frequently leads to resolution or a marked dimunition in neurologic symptoms within 24 to 48 hours.

The long-term outcome of acute stroke is variable; many patients lack significant motor impairment but may demonstrate impaired executive functioning. A second stroke is very likely without the use of regular RBC transfusions to suppress the Hgb S percentage, and even with a chronic transfusion regimen (see below), ~20% of acute stroke victims will experience a second acute stroke. For this reason, hematopoietic stem cell transplantation (HSCT) may be an optimal therapy for children who have a history of acute stroke when a suitable donor is available (see below).

PRIMARY STROKE PREVENTION. The terrible burden of acute stroke in patients with SS and Sβ^0 has driven research dedicated to primary stroke prevention. In the early 1990s, transcranial Doppler (TCD) ultrasonography was shown to predict risk of acute stroke in SS and Sβ^0, with an abnormal TCD examination representing a 40% risk of stroke in the subsequent 3 years. In the landmark Stroke Prevention Trial in Sickle Cell Anemia, children identified to be at high risk by TCD were randomly assigned to monthly blood transfusions versus

observation, with a 90% decrease in the rate of stroke observed in the transfusion group. (9) Hence, annual screening with TCD has become standard care for children with SS and Sβ^0. The duration of transfusion is indefinite, although current studies are addressing whether patients may be transitioned safely to HU to prevent stroke.

SILENT STROKE. In the past decade, silent stroke has been recognized as an important problem in children with SS and Sβ^0. Silent stroke is defined by the presence of findings on MRI suggestive of old cerebral infarction, typically small areas of gliosis, without a corroborating clinical history of acute stroke symptoms. Silent strokes are associated strongly with neurocognitive deficits and are a risk factor for subsequent acute stroke. Most studies have revealed that silent strokes occur in ~30% of children (10) with SS and Sβ^0, leading to estimates of the cumulative prevalence of central nervous system infarct events (acute and silent stroke) of ~40% in this population. Regular blood transfusions are under study to determine whether they may decrease the risk of acute stroke in patients who have experienced silent stroke.

COGNITIVE IMPAIRMENT. Not surprisingly, patients with SCD with a history of acute stroke or silent stroke have high rates of neuropsychological dysfunction. Even the SCD population that has not been affected by acute or silent stroke has a high rate of a neuropsychological dysfunction that worsens with age, including deficits in general intelligence, attention and executive functioning, memory, language, and visual-motor performance compared with matched controls. The result may be difficulty at school and in other tasks requiring executive functioning. Early evaluation and intervention in school settings may improve outcomes for this at-risk population.

Other Clinical Sequelae

Splenic Sequestration

Rapid enlargement of the spleen with resultant trapping of the blood elements is known as acute splenic sequestration and occurs in ~30% of children with SS by 5 years of age, with most first episodes occurring before 2 years of age. Children with SC disease tend to develop splenic sequestration at 10 years of age or older. Splenic sequestration was a common cause of mortality among children with SCD before the 1980s. Education of family members in daily spleen palpation is now standard care and has increased the detection of sequestration and markedly decreased mortality.

Evaluation of a child with splenic sequestration will reveal splenomegaly, a Hgb value below baseline, and thrombocytopenia, because all blood elements will be trapped in the enlarged spleen. The management of an initial splenic sequestration episode typically includes cautious transfusion to Hgb values between 7 and 9 gr/dL. A reduction in spleen size frequently occurs 1 to 3 days after initial presentation and may lead to 2 to 3 gr/dL increases in Hgb, a phenomenon known as "auto-transfusion."

Approximately one-half of patients will experience recurrence of splenic sequestration. Splenectomy is performed commonly after a second or third sequestration episode, although some centers chronically transfuse affected infants until 2 years of age before undertaking splenectomy.

Cholelithiasis

SCD is a chronic hemolytic anemia, and when Hgb is released from the RBC, bilirubin is produced, leading to jaundice. Ultimately, this increased bilirubin is stored in the gall bladder and can precipitate to form stones. Presenting signs and symptoms of cholelithiasis in SCD include right upper quadrant or epigastric abdominal pain, jaundice, and vomiting. Incidentally discovered, asymptomatic gallstones may be observed without requiring intervention. Symptomatic stones or stones obstructing the common bile duct commonly require cholecystectomy. A laparoscopic approach is now standard for cholecystectomy, which reduces the duration of postoperative pain and hospitalization. See below for additional notes on the surgical management of patients with SCD.

Priapism

Priapism is a prolonged, painful erection of the penis with typical onset in the early morning hours. It can occur in two forms: prolonged, an episode of ≥4 hours duration, and stuttering, self-limited episodes that can occur in clusters. In SCD, priapism is thought to be caused by sickling of RBCs in the corpora cavernosa of the penis, leading to sludging and an increase in intrapenile pressure. (11) This effect, in turn, leads to local acidosis and worsening deoxygenation, which leads to further sickling in a vicious cycle that causes further outflow tract obstruction and severe pain.

Priapism can occur as young as 3 years of age, and ~30% of boys will have an episode by age 15. If a prolonged episode is left untreated, fibrosis of the cavernosa may develop, leading to permanent erectile dysfunction. Treatment of an acute episode of priapism may include

aggressive analgesia and pharmacologic efforts to decrease the vascular engorgement of the cavernosa through agents such as pseudoephredrine and etilefrine. Aspiration and irrigation of the cavernosa by a urologist may be necessary for prolonged episodes. Blood transfusions and oxygen are of unproven benefit for acute episodes of priapism.

Prevention of priapism is understudied, although nightly pseudoephedrine or etilefrine have been reported to achieve some success in case series or uncontrolled trials. Gonadotropin releasing hormone analogs also have been used to prevent recurrent priapism. The effects of HU and chronic blood transfusion for prevention of priapism are largely unreported.

Surgery

Major surgery places a child with SCD at risk of complications, including ACS. To that end, perioperative transfusion to increase the Hgb concentration and decrease the Hgb S percentage is considered standard care for major surgeries. Additionally, measures such as incentive spirometry, carefully titrated analgesia, oxygen therapy, and close inpatient observation may help decrease the risk of postoperative SCD-related complications. The role of preoperative transfusion for minor surgery including tonsillectomy/adenoidectomy is controversial, but transfusion may be safely avoided for some patients undergoing such procedures.

Therapeutics

Hydroxyurea

HU is the only medication approved by the Food and Drug Administration for the treatment of SCD. HU use for children with SCD has been reviewed recently. (12) HU was developed originally as a chemotherapeutic agent for certain leukemias and myeloproliferative diseases, but in the early 1980s, HU was recognized to increase expression of fetal Hgb. Fetal Hgb was known to inhibit the polymerization of HgbS, the primary mechanism underlying the SCD pathogenesis. HU also may act through a relative myelosuppression with a decrease in circulating neutrophils, cells whose role in the pathogenesis of some SCD complications has recently been recognized.

In clinical trials for adults with SCD, HU was shown to markedly reduce the rate of VOCs, ACS, blood transfusions, and all-cause hospitalizations. In addition, long-term follow-up studies have revealed HU to confer a survival advantage for adults with SS and $S\beta^0$. In children with SCD, the published experience with HU is less extensive, although clinical trials with HU have been conducted in children as young as 9 to 18 months of age.

A randomized clinical trial of HU for infants with SCD (BABY-HUG) was completed recently. (13) Although HU failed to improve the primary outcomes of kidney and spleen function, a decrease was observed in the rates of hospitalization, blood transfusion, ACS, dactylitis, and other VOCs for infants on HU compared with those on placebo. There is also some evidence that HU may reduce conditional and even abnormal TCD velocities.

The toxicity profile for HU has shown it to be tolerable with minimal toxicities other than the risk of mild myelosuppression. Thus, regular monitoring of blood counts is required while on HU. HU is theorized to be a teratogen as well and is contraindicated in pregnant women. Some concerns have existed in both the patient and clinician community that HU, as a chemotherapeutic agent, may induce genetic changes that could lead to myelodysplasia, leukemia, or other malignancy, yet these complications have never been attributed to HU in an actual patient with SCD. Importantly, recent analyses of peripheral blood mononuclear cells have not demonstrated impaired DNA repair mechanisms or increased mutations in children on HU compared with other patients with SCD.

In summary, HU is an important therapeutic option for children with SCD. Historically, HU was reserved only for children with severe or frequent complications of SCD, but as suggested by the authors of the recently published BABY-HUG study, consideration must now be given to offering HU to all children with SS or $S\beta^0$. (13)

Chronic Transfusion

The suppression of endogenous RBC production by regular transfusion of donor RBCs is another means by which complications of SCD may be ameliorated. The clearest indications for chronic transfusions are for both primary and secondary stroke prevention. Short- and long-term chronic transfusions also have been used to treat complications such as frequent pain, severe or frequent ACS, and growth failure, among others. Simple transfusion is the most commonly used method for RBC delivery in chronic transfusions. This method carries with it the ubiquitous problem of iron overload, because each milliliter of transfused blood contains between 0.5 and 1 mg of elemental iron, which approximates normal daily absorption. Iron loading occurs primarily in the liver, heart, and endocrine glands in patients with

SCD, and severe overload can result in morbidity and mortality.

The treatment of iron overload requires an exogenous iron chelator because humans lack a mechanism to increase excretion of the excess iron. Before 2007, the only available iron chelator (deferroxamine) in the United States required subcutaneous administration for 10 to 12 hours per day, 5 to 7 days per week. Adherence to such a medication regimen was understandably low, so severe iron overload developed in many chronically transfused patients with SCD. In 2007, an oral iron chelator (deferasirox) was licensed. Deferasirox appears to be as efficacious as deferroxamine in reducing iron burden.

In addition to iron overload, transfusion-related infection and alloantibody formation are other potential complications of chronic transfusions. Improved donor selection policies and careful nucleic acid based-testing have greatly reduced, but not eliminated, the likelihood of transfusion-related infection. The risk of alloantibody formation may be mitigated by extended RBC cross-matching and programs to match donors and recipients by race and ethnicity. Exchange transfusion, either by manual exchange or erythrocytopheresis, is an alternative to simple transfusion and appears to greatly decrease iron loading in patients on chronic transfusions.

Hematopoietic Bone Marrow Transplantation

HSCT remains the only curative option for children with SCD. Transplantation works by replacing sickle erythrocyte progenitors with normal erythrocyte progenitors in the bone marrow. HSCT typically is reserved for patients affected by severe or life-threatening complications of SCD, including stroke and ACS.

The most important risks of HSCT include peri-transplant mortality (frequently from infection), graft-versus-host disease, graft failure, and conditioning-induced infertility. Limitations to the use of HSCT include a paucity of matched siblings and poor representation of minorities in the bone marrow donor pool. Unrelated HSCT and reduced intensity conditioning regimens have been published recently but require further exploration in the clinical trial setting.

Emerging Therapeutics

Recently, a variety of new therapies have been suggested for SCD. Most tantalizing is the potential of gene therapy via the insertion of a normal β globin or γ globin gene into a patient's own hematopoietic precursors. Bone marrow has been the traditional source of hematopoietic stem cells, although the recent recognition that pluripotent stem cells may be induced from skin cells may make the production of corrected hematopoietic precursors less invasive and painful. Other emerging therapeutics currently under development for patients with SCD include novel agents aimed at inducing HgF expression, novel anti-inflammatory or antithrombotic agents to treat or prevent sickle cell complications, inhaled nitric oxide, HSCT from unrelated donors, and reduced intensity conditioning for HSCT, among others.

Quality of Care

The provision of care to patients with SCD in the United States occurs within a complex tapestry of societal and personal interactions. The acute complications of SCD lead to frequent emergency department visits and hospitalizations for some patients. Unfortunately, studies of patient experiences and clinician attitudes in both the emergency department and inpatient settings have demonstrated frequent distrust between patients and providers. Patients describe both over- and undertreatment and lack of involvement in decision-making.

The quality-of-care provided varies depending on the rarity and severity of a given complication and the experience of the hospital and its personnel with SCD patients. Recently, the first set of rigorously developed quality-of-care indicators for children with SCD were published. (14) These indicators establish a benchmark that will allow providers and health-care organizations to measure their performance in SCD care, and as changes are made to improve performance, the SCD patient's experience of care also may begin to improve.

Prognosis and Survival

In spite of the many complications that may afflict children who have SCD, their prognosis has improved in past decades. Before routine newborn screening and pneumococcal prophylaxis, death from IPD, splenic sequestration, ACS or other severe complications of SCD was a common occurrence in childhood. Recent studies from cohorts in the United States and the United Kingdom suggest that death in childhood is becoming an infrequent event, with ~95% of children with SCD surviving to age 18 years. (15) Unfortunately, the young adult years, following transition to adult care, appear to be a high-risk period for individuals with SCD, which has led to a recent emphasis on improving the transition process, with the long-term goals of improving quality of life, quality of medical care, and survival for patients with SCD.

Summary

- Sickle cell disease (SCD) is a heterogeneous group of prevalent, potentially life-threatening, chronic disorders of hemoglobin (Hgb).
- Hgb polymerization underlies the pathophysiology of SCD.
- Children who have SCD benefit from regular health maintenance visits with a pediatric hematologist and a primary care pediatrician.
- The high incidence of invasive pneumococcal disease (IPD) in SCD justifies newborn screening, daily prophylactic penicillin, and immunization with the pneumococcal conjugate and polysaccharide vaccines.
- Vaso-occlusive pain crises are the clinical hallmark of SCD and occur with increasing frequency through childhood. These episodes warrant aggressive treatment with analgesics and hydration and may be prevented with hydroxyurea (HU) therapy.
- Annual transcranial Doppler (TCD) screening for patients ages 2 to 16 years identifies those at high risk for acute stroke, and regular blood transfusions can reduce this risk greatly.
- Common indications for initiating HU therapy have been severe or frequent vaso-occlusive crises or acute chest syndrome, but this therapy may be considered in younger and less symptomatic patients.
- The prognosis for children with SCD has improved, with the vast majority surviving into adulthood, prompting a focus on improving the process of transition to adult care.

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PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with 2012 *Pediatrics in Review*, *AMA PRA Category 1 Credit™* can be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. Neonatal screening has identified an infant with sickle cell anemia. Which of the following is the most appropriate method of protection against invasive pneumococcal disease?
   - A. Begin daily prophylactic penicillin at 2 years of age; administer pneumococcal polysaccharide vaccine instead of pneumococcal conjugate vaccine at recommended intervals for all children.
   - B. Begin daily prophylactic penicillin at 2 years of age; pneumococcal conjugate vaccine as recommended for all children, and at least two doses of pneumococcal polysaccharide vaccine at 2 and 5 years.
   - C. Begin daily prophylactic penicillin before 2 months of age; administer pneumococcal conjugate vaccine as recommended for all children and at least two doses of pneumococcal polysaccharide vaccine at 2 and 5 years.
   - D. Begin daily prophylactic penicillin before 2 months of age; administer pneumococcal conjugate vaccine instead of pneumococcal polysaccharide vaccine at recommended intervals for all children.
   - E. Begin daily prophylactic penicillin before 2 months of age; administer pneumococcal polysaccharide vaccine at 2, 4, and 6 months of age and at least two doses of pneumococcal conjugate vaccine at 2 and 5 years.

2. A 3-year-old girl with sickle cell anemia presents with fatigue and malaise for the last 3 days. Her mother feels that the girl appears much paler than usual. Examination reveals a pale child with temperature 37.4°C, heart rate 125 beats per minute, respirations 28 per minute, and blood pressure 90/50 mm Hg. The rest of the physical examination is unremarkable. Complete blood count reveals a hemoglobin level of 4 G/dL, WBC 5,400/μL with 34% neutrophils, 48% lymphocytes, and 18% monocytes, and platelets 250,000/μL. Reticulocyte count is 0.4%. Which of the following best explains this child's anemia?
   - A. Excessive lysis of irreversible sickle cells.
   - B. Impaired release of erythrocytes from bone marrow.
   - C. Maturation arrest of erythrocyte precursors in the bone marrow.
   - D. Replacement of bone marrow with monocytes.
   - E. Sequestration of erythrocytes in spleen.

3. A 4-year-old girl with sickle cell disease (genotype $S\beta^0$) presents with excruciating pain in both lower extremities for the last 12 hours. She describes her pain as 9/10 below the right knee and 6/10 below the left knee. She has a pet turtle, and her immunization record is unavailable. Physical examination reveals temperature 38.6°C, respirations 26 per minute, heart rate 110 beats per minute, and blood pressure 110/78 mm Hg. There is mild erythema and moderate swelling over the upper medial surface over right tibia with point tenderness. Which of the following is the most important risk factor for this presentation?
   - A. Elevated fetal hemoglobin concentration.
   - B. Genotype $S\beta^0$.
   - C. Having a turtle as a pet.
   - D. Inadequate immunization.
   - E. Low baseline hemoglobin.

4. A 7-year-old boy with sickle cell disease (genotype SS) presents with dysphasia and right-sided weakness. Physical examination reveals normal vital signs. There is depression of right angle of mouth and weakness of right upper and lower extremities. Which of the following annual screening tests would have been most helpful in predicting the risk of this complication?

   A. Comprehensive examination by neurologist.
   B. Computed tomography of head.
   C. Magnetic resonance imaging of head.
   D. Measurement of hemoglobin S percentage.
   E. Transcranial Doppler ultrasonography.

5. A 15-year-old boy with sickle cell disease (genotype SS) has had several vaso-occlusive crises. Which of the following statements after treatment with hydroxyurea for this patient is most accurate?

   A. Baseline hemoglobin level will be lower.
   B. Cellular DNA repair mechanisms are impaired.
   C. Increased circulating neutrophil numbers will offer protection against bacterial infection.
   D. Increased expression of fetal hemoglobin will occur.
   E. Transcranial Doppler velocities will increase.

Condolences

The staff of *Pediatrics in Review* has lost another special colleague and friend. Dr. Gregory Liptak, a skilled and compassionate developmental pediatrician and member of our Editorial Board, died on March 3, 2012, and will be missed by all of us.

Inborn Errors of Metabolism: Part 1: Overview

Paul A. Levy, MD*

Author Disclosure
Dr Levy did not disclose any financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Recognize the signs and symptoms that are suggestive of an inborn error of metabolism.
2. Describe the characteristics of different classes of metabolic syndromes.
3. Formulate a logical diagnostic approach to determining which specific condition is present when an inborn error of metabolism is suspected.
4. Delineate the value and scope of newborn screening programs.
5. Be aware of treatment modalities for inborn errors of metabolism.

Introduction

As hospitalizations for traditional pediatric illnesses have declined during the last century, due primarily to improved treatment of infectious diseases, the contribution of other disorders has gained prominence. Biochemical genetics, with its various inherited metabolic disorders (inborn errors of metabolism), has become more important in the routine care of hospitalized pediatric patients. Newborn screening also is contributing to the increased awareness of inherited metabolic disorders. Only a few years ago, most states tested for only as many as eight disorders, generally including phenylketonuria, galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, sickle cell disease, hypothyroidism, and congenital adrenal hyperplasia. Recent changes in technology have permitted an increase in the number of disorders tested. A national panel has recommended expanding the testing to 29 disorders, but many states already have begun to screen for more than 40 different disorders with the new technology of tandem mass spectrometry. This expanding list includes amino acid disorders, organic acid disorders, urea cycle diseases, and fatty acid oxidation defects. Some states are working to add lysosomal storage diseases and peroxisomal disorders to their newborn screening panels.

Pediatricians need to recognize and become familiar with these diseases not only to help with the diagnosis but also to help educate parents and advocate for patients. Some patients may fall ill with inherited metabolic disorders not currently detected by newborn screening; others may have conditions that were missed on their newborn screens. Affected children may present at a few days to a few months of age with lethargy or vomiting and be thought to have sepsis or shock. Other disorders may present at a later age with a more indolent picture of developmental delay or regression.

Attempts have been made at developing a rational framework for conceptualizing inherited metabolic diseases, but there is no one simple method of categorizing all of the inherited metabolic diseases with their many different presentations and various ages of onset.

This review is in two parts. The article that appears in print offers a simplified approach to diagnosis and a discussion of the presentation of and testing for many groups of inherited metabolic disorders. The second part appears online only and provides a more detailed discussion of the various groups of inherited metabolic disorders.

Abbreviations

CDG:	congenital disorders of glycosylation
GSD:	glycogen storage disease
KGDH:	alpha-ketoglutarate dehydrogenase
MPS:	mucopolysaccharidosis
MRI:	magnetic resonance imaging
OXPHOS:	oxidative phosphorylation
PCD:	pyruvate carboxylase deficiency
PDD:	pyruvate dehydrogenase deficiency

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Table 1. **Inborn Errors of Metabolism Associated With an Acute Crisis**

Diagnostic Clues		
Primary	Secondary	Suggested Disorders
Acidosis	± Hypoglycemia ± Lactic acidosis ± Ketosis ± Elevated ammonia Increased anion gap	Various organic acid disorders
	Significant lactic acidosis Normoglycemia	Mitochondrial disorders Pyruvate dehydrogenase deficiency Alpha-ketoglutarate dehydrogenase deficiency Pyruvate carboxylase deficiency
	Significant lactic acidosis Hypoglycemia	Glycogen storage type I Fructose-1,6-bisphosphatase deficiency
	Normal anion gap Normal lactate No ketosis	Renal tubular acidosis
Hyperammonemia	Alkalosis or normal pH Normal lactate	Urea cycle disorders
	Reye-like illness (hypoglycemia, elevated liver transaminases, normal ketones)	Fatty acid oxidation defects
	Acidosis ± Lactic acidosis ± Ketosis ± Hypoglycemia Increased anion gap	Various organic acid disorders
Hypoglycemia	Acidosis ± Ketosis ± Lactic acidosis ± Increased ammonia Increased anion gap	Various organic acid disorders
	Hepatomegaly ± Lactic acidosis	Glycogen storage disorders
	No ketosis No acidosis Normal lactic acid	Hyperinsulinemia Fatty acid oxidation defects
	Hyponatremia Hypotension	Adrenal insufficiency
	Signs of liver failure	Tyrosinemia Glycogen storage disease type IV Galactosemia Niemann Pick type C

Approach to Diagnosis and Testing

In general, inherited metabolic disorders can be divided into two groups: disorders that can present with an acute crisis (Table 1), often with encephalopathy, and disorders that have a more chronic, indolent course (Table 2). Two authors have made significant contributions to help clinicians identify and diagnose inherited metabolic disorders. Jean Marie Saudubray (*The Molecular and Metabolic Bases of Inherited Disease*. 8th ed. New York, NY: McGraw Hill; 2001, updated online at www.ommbid.com) and JTR Clarke (*A Clinical Guide to Inherited Metabolic Diseases*. 2nd ed. New York, NY: Cambridge University Press; 2002) have described frameworks for the evaluation of these diseases. This review provides a simplified overview, but readers are encouraged to consult these references for additional assistance in diagnosing inherited metabolic disorders.

Acute Presentation

Children who have inherited metabolic disorders almost always appear normal at birth because the metabolic intermediate that is responsible for the disorder frequently is a small molecule that can traverse the placenta and be eliminated by the mother's metabolism. Once the

Table 2. Findings Suggestive of a Chronic Metabolic Disorder

Neurologic
Developmental delay (especially with regression), seizures (myoclonic or partial complex), seizures resistant to anticonvulsant therapy, deafness, blindness, stroke, or movement disorder (dystonia, chorea)
Liver
Hepatosplenomegaly, cholestasis, liver failure (± cirrhosis), hypoglycemia
Heart
Cardiomyopathy (dilated or hypertrophic), arrhythmias
Kidney
Enlarged kidneys with microcysts, renal failure, tubular dysfunction, generalized amino aciduria, hypophosphatemia, rickets
Muscle
Peripheral muscle weakness, myoglobinuria
Eye
Cataracts, corneal opacities, lens dislocation, retinal abnormalities (cherry red spots, retinitis pigmentosa), ophthalmoplegia, strabismus
Dysmorphic Features
Macrocephaly, high forehead, large anterior fontanelle, coarsened facial features, large jaw, small jaw, large ears, abnormal fat distribution

infant is born, symptoms begin to appear after a variable period of time (days, weeks, months, or rarely, years) as the metabolite accumulates.

An acute presentation is most common in infants and young children. Infants have a limited repertoire with which to respond to an overwhelming illness. Generally, they manifest poor feeding and lethargy. Trying to distinguish a routine childhood illness from an inherited metabolic disorder can be difficult. Even if there is vomiting, respiratory distress, and eventually encephalopathy (coma), such symptoms most commonly are attributed to infection and sepsis, not to an inherited metabolic disorder. Routine blood tests, cultures, and chest radiographs yield unremarkable results. An important clue that should stimulate the clinician to look further is the lack of improvement with standard therapy.

Organic acidemias, urea cycle defects, and some disorders of amino acid metabolism can result in acute encephalopathy. An inherited metabolic disorder always should be considered in the differential diagnosis, especially if there are no associated risk factors for infection. Consideration of these disorders may require some diagnostic suspicion, but identifying them requires only a few laboratory tests.

When presented with a child who has acute encephalopathy, the clinician must determine the pH, lactate value, electrolyte concentrations, liver function, and glucose status of the patient. Ammonia should be measured for any ill child who has unexplained lethargy or vomiting. The presence of ketones in the urine also may be important. The results of such tests can help to diagnose an underlying inherited metabolic disorder.

Acidosis

The presence of acidosis (pH <7.30, P_{CO_2} <30 torr, and HCO_3^- <15 mEq/L [15 mmol/L]) indicates significant disturbance of normal metabolism and may result from infection, dehydration, intoxication, or anoxia as well as from an inborn error of metabolism. Organic acid disorders present with acidosis due to the accumulation of acidic metabolites. Hypoglycemia, lactic acidosis, ketosis, and a mild to moderately elevated ammonia value also may be present, either individually or together. The presence or absence of these other findings may help distinguish among different organic acidemias.

If hypoglycemia is present with lactic acidosis but no significant ketosis, disorders of gluconeogenesis should be investigated. Significant lactic acidosis may suggest the possibility of an energy production disorder, either a mitochondrial defect of oxidative phosphorylation (OXPHOS), pyruvate dehydrogenase deficiency (PDD), alpha-ketoglutarate dehydrogenase (KGDH) deficiency, or pyruvate carboxylase deficiency (PCD). Finally, acidosis without the elevation of lactate or the presence of ketosis and a normal anion gap suggests renal tubular acidosis.

LACTIC ACIDOSIS. Lactic acidosis often results from hypoxia or poor perfusion, which may be caused by dehydration. Glycogen storage diseases, pyruvate metabolism defects (PDD, PCD, KGDH), fructose-1,6-bisphosphatase deficiency, and mitochondrial OXPHOS abnormalities increase lactic acid production directly; organic acid disorders may cause a secondary rise in lactate. In many hospitals, it is relatively simple to measure lactic acid on a blood gas determination. Such testing is optimal because it provides both the pH and the lactate values quickly. Determination of the lactic

acid value helps with the diagnosis of organic acidurias and glycogen storage diseases.

For other disorders, it may be beneficial to measure pyruvate, but this determination is more difficult because the blood must be drawn and placed immediately into a special tube. Generally, the result is not available immediately. An increased lactic acid value with a lactic acid-to-pyruvate ratio of less than 25 is normal, but the elevated lactic acid suggests a defect in pyruvate dehydrogenase or an enzyme of gluconeogenesis (fructose-1,6-bisphosphatase or glucose-6-phosphatase). An increased ratio (>30) suggests a deficiency of pyruvate carboxylase or KGDH or an OXPHOS defect. Determination of blood ketones (3-hydroxybutyrate and acetoacetic acid) helps to delineate the defect further. A ratio of 3-hydroxybutyrate-to-acetoacetic acid greater than 2:1 is suggestive of an OXPHOS defect.

KETOSIS. Ketosis is a normal physiologic response in some circumstances, but it is not normal when it is severe enough to cause acidosis. Neonates do not generate ketones well, so the presence of ketones in a newborn's urine is of concern. Many organic acidurias present with ketosis. Persistent ketosis with normal urine organic acids suggests a defect in one of two ketolytic enzymes.

HYPERAMMONEMIA. Ammonia values may be elevated in a number of disorders, including urea cycle defects, some organic acidemias, and fatty acid oxidation defects that may present with a Reye-like syndrome (vomiting, elevated liver transaminases, hyperammonemia, coma). The organic acid disorders can be distinguished by the presence of acidosis. Fatty acid oxidation defects generally create hypoglycemia, which the urea cycle defects do not.

HYPOGLYCEMIA. When hypoglycemia is an isolated finding, hyperinsulinism should be considered. Hypoglycemia also can be associated with liver failure, so both metabolic disorders (tyrosinemia, glycogen storage disease [GSD] type IV, galactosemia, and Niemann-Pick disease type C) as well as congenital malformations and acquired conditions should be ruled out. If the hypoglycemia is associated with hepatomegaly (± lactic acidosis), glycogen storage diseases (GSD I, III, VI, and IX) and fructose-1,6-bisphosphatase deficiency are likely. When acidosis or ketosis is present with hypoglycemia, the organic acidurias are a likely cause. Hypoglycemia without ketosis (beyond the newborn period) should prompt investigation for a fatty acid oxidation defect. Lastly, hypoglycemia with hyponatremia and hypotension may be a presentation of adrenal insufficiency, especially in patients who have been receiving steroids chronically.

Treatment of Encephalopathy

Presentation of an infant or young child in an encephalopathic coma requires urgent treatment in an attempt to avert or mitigate neurologic sequelae and potential death from a treatable cause. Recognizing the possibility that an inborn error of metabolism may be responsible should prompt appropriate laboratory tests (ammonia, lactic acid, urine organic acids, plasma and urine amino acids, pH, glucose, liver function tests, pyruvate, acylcarnitine profile). The results of these tests may not be immediately available, but they should be completed in 48 to 72 hours. Treatment can begin before a definitive diagnosis is determined.

An elevated ammonia concentration without acidosis is presumed to be a urea cycle defect. Immediate arrangements for hemodialysis should be made and ammonia removal medications (sodium benzoate and sodium phenylacetate) and arginine administered. All protein intake should be halted if a urea cycle defect or a disorder related to protein "intolerance" such as an organic acidemia is suspected. Such protein deprivation cannot be undertaken without providing appropriate caloric intake from carbohydrate (10% glucose) and an intravenous fat emulsion. If the caloric intake is not sufficient, catabolism of the patient's protein occurs, raising ammonia concentrations in a urea cycle disorder or presenting substrate for the organic acidurias.

A number of inherited metabolic disorders respond to large ("mega") doses of the cofactors of their respective enzymes. Presumptively, a "cocktail" of such cofactors can be started for a possible inherited metabolic disorder. Vitamin B_{12} (hydroxycobalamine) (1 mg/day intramuscularly), thiamine (50 mg orally BID), biotin (10 mg orally BID), riboflavin (50 mg orally BID), folic acid (10 mg orally BID), and carnitine (100 mg/kg per day orally divided QID) have been found to be effective for a number of disorders and should be administered. Patients who experience hypoglycemia should be given glucose to maintain normal plasma concentrations. Treatment can be tailored as the results of testing become available and a diagnosis is made.

Chronic Disorders

The second group of metabolic disorders is characterized by a more chronic course. They are difficult to recognize and diagnose because their onset may be from birth to adulthood and they have myriad signs and symptoms. The presence of some clinical findings helps to organize

the group into more manageable subgroups. The first and largest subgroup is disorders that create neurologic abnormalities. Involvement of a specific organ system may suggest a specific inherited metabolic disorder and comprise the second subgroup. The third subgroup is defined by the presence of dysmorphic features, which although not common to many inherited metabolic disorders, can be a helpful distinguishing feature.

Neurologic

Neurologic findings may include developmental or psychomotor delay, seizures, movement disorders, deafness, and blindness. Psychomotor or developmental delay is the most common clinical finding of inherited metabolic disorders. Not all children who exhibit developmental delay, however, have inherited metabolic disorders. Developmental delay due to an inherited metabolic disorder usually is global (rather than an isolated delay of speech, for example) and shows loss of milestones (regression) over time as the disease progresses.

Seizures, if they occur, are of various types, with electroencephalographic findings that may be difficult to classify into a specific seizure syndrome. Seizures (often myoclonic or partial complex) that are resistant to anticonvulsant therapy may suggest an underlying inherited metabolic disorder.

Movement disorders associated with inherited metabolic disorders include dystonias (abnormal muscle contractions that result in abnormal postures and involuntary torsional movements) and choreas (involuntary movements that can be athetotic and involve twisting or torsional movements).

Although there may be some overlap, involvement of either gray matter or white matter may help in narrowing the differential diagnosis of the underlying disorder. Disorders involving the cerebral gray matter tend to occur early in life. In addition to developmental delay, patients who have these conditions may exhibit seizures, a movement disorder (chorea or dystonia), hearing loss, or blindness (cortical or due to optic atrophy). Magnetic resonance imaging (MRI) findings may show only some cerebral atrophy or be read as normal. Neuronal lysosomal storage diseases can be considered in such patients as well as some of the mitochondrial disorders.

Disorders involving the cerebral white matter generally have abnormalities of tone (hypotonia or hypertonia) and motor difficulties (sometimes delayed or loss of motor milestones). This group includes the leukodystrophies, which, by definition, have abnormal white matter, and Canavan disease, Alexander disease, and some of the lysosomal storage disorders.

Some inherited metabolic disorders may result in neuronal migration defects. These conditions include peroxisomal disorders and some congenital disorders of glycosylation.

Stroke, an unusual finding in children, should suggest homocystinuria and the mitochondrial disorder MELAS (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes). Fabry disease and some forms of congenital disorders of glycosylation (CDG) also have been associated with stroke.

Other Specific Organ System Involvement

LIVER OR SPLEEN. Liver involvement may lead to hypoglycemia, cholestasis, or liver failure with cirrhosis. Disorders that lead to cirrhosis include tyrosinemia, classic galactosemia, hereditary fructose intolerance, the Zellweger spectrum of peroxisomal disorders, CDG, alpha-1-antitrypsin deficiency, Wilson disease, and mitochondrial disorders. Hypoglycemia may result from a GSD or a fatty acid oxidation defect as well as some organic acidurias. Lysosomal storage diseases, especially the mucopolysaccharidoses (MPSs), are characterized by hepatosplenomegaly and also present with dysmorphic (coarsened) features, intellectual disability, and short stature.

HEART. Some fatty acid oxidation defects may present with severe cardiomyopathy. Other disorders that have significant cardiac symptoms include carnitine transport disorders, Pompe disease (GSD type II), Fabry disease, G_{M1} gangliosidosis, CDG, and some mitochondrial diseases.

KIDNEY. Glutaric aciduria type II may cause enlarged kidneys that contain small microcysts and are detected at birth. Galactosemia and hereditary fructose intolerance with chronic exposure to fructose lead to proximal tubule dysfunction and kidney failure if left untreated. Tyrosinemia type I generally manifests tubular dysfunction, which results in hypophosphatemia and rickets. Cystinosis is associated with decreased glomerular function leading to end-stage renal failure. Fanconi syndrome (aminoaciduria) also may be caused by some mitochondrial diseases.

MUSCLE. Peripheral muscle weakness is characteristic of the muscle forms of GSD, generally appearing in older children and sometimes accompanied by myoglobinuria. Mitochondrial disease may cause muscle weakness with or without persistent lactic acidosis.

EYE. Ocular findings often provide a clue to an underlying inborn metabolic disorder. The presence of cataracts may suggest galactosemia, peroxisomal disorders, Lowe syndrome, alpha-mannosidosis, galactokinase deficiency, mitochondrial respiratory chain disorders, sialidosis, lysinuric protein intolerance, Sjögren-Larsson syndrome, and Wilson disease. In adults, patients who have Fabry disease or homocystinuria and carriers for both Lowe syndrome and galactosemia (galactose-1-phosphate uridyltransferase deficiency and uridine diphosphate galatose-4-epimerase) also may develop cataracts.

Corneal abnormalities such as opacities can be seen in MPS I and VI, Wilson disease, galactosialidosis, cystinosis, Fabry disease, and tyrosinemia (ocular form). Homocystinuria and Marfan syndrome are associated with lens dislocation, as are molybdenum cofactor deficiency, sulfite oxidase deficiency, contractural arachnodactyly, and Marshall syndrome. Cherry red spots are found in a number of lysosomal storage diseases due to the accumulation of storage material in the retina, which causes paleness but a normal-appearing fovea, resulting in a central "spot." This finding is associated with Tay-Sachs disease (G_{M2} gangliosidosis), G_{M1} gangliosidosis, sialidosis, Niemann-Pick disease, Farber disease, galactosialidosis, and metachromatic leukodystrophy.

Mitochondrial disease (Leigh syndrome, Kearns-Sayre syndrome), chronic progressive external ophthalmoplegia, and neurogenic weakness ataxia retinitis pigmentosa may be associated with retinitis pigmentosa as well as with weakness of the extraocular muscles leading to ophthalmoplegia. Other inherited metabolic disorders associated with retinitis pigmentosa include congenital disorders of glycosylation, ceroid lipofuscinoses, and peroxisomal disorders.

SKIN. Biotinidase deficiency often presents with alopecia and a rash (usually eczemalike). Angiokeratomata characteristically are seen in Fabry disease, but also can be seen in fucosidosis, beta-mannosidosis, galactosialidosis, and aspartylglucosaminuria. Menkes syndrome is known for hair abnormalities (soft, pale, brittle, and wiry), but patients afflicted with arginosuccinic aciduria and citrullinemia also may have brittle hair.

Farber lipogranulomatosis (a sphingolipidosis) has unique periarticular subcutaneous nodules and also is characterized by joint swelling and contractures.

DYSMORPHIC FEATURES. Although not typical of most inherited metabolic disorders, dysmorphic features can be a helpful diagnostic clue. The largest group of disorders associated with dysmorphic features is the lysosomal storage diseases. MPSs are the most identifiable members of this group and present with coarsened facial features, hepatosplenomegaly, and short stature. Other lysosomal disorders that present with dysmorphic features include some of the oligosaccharidoses (mannosidosis, galactosialidosis, aspartylglucosaminuria, sialidosis, and I-cell disease), which can involve features similar to those of the MPS disorders. G_{M1} gangliosidosis (a sphingolipidosis) also presents with MPS-like facial features. Farber lipogranulomatosis presents with dysmorphic features and characteristic periarticular subcutaneous nodules.

Only a few disorders present at birth or soon after with dysmorphic features: some of the lysosomal storage disorders, Sly syndrome, sialidosis, galactosialidosis, G_{M1} gangliosidosis, and Krabbe disease, as well as Pompe disease, which is a lysosomal disorder, although usually included with the GSDs. Peroxisomal disorders generally are associated with dysmorphic features characterized by the Zellweger spectrum (high forehead, flat occiput, large anterior fontanelle, hypoplastic supraorbital ridges, epicanthal folds, broad nasal bridge, anteverted nostrils, and micrognathia). Finally, many of the CDG exhibit dysmorphic features (large ears, strabismus, abnormal fat distribution).

Evaluation

Evaluation for a possible inherited metabolic disorder in the chronic group begins with a developmental assessment and history. If an inherited metabolic disorder is suspected, a fairly extensive initial screen includes MRI of the brain; a skeletal survey; testing for plasma amino acids, urine organic acids, urinary mucopolysaccharides, and oligosaccharides; transferrin electrophoresis; measuring very long-chain fatty acids, pH, lactate, and ammonia; verifying results of the newborn screen; and obtaining an acylcarnitine profile and an ophthalmologic examination.

The MRI should help distinguish gray and white matter involvement as well as cerebellar hypoplasia (CDG) and neuronal migration defects (CDG and peroxisomal disorders). A skeletal survey may uncover evidence of dysostosis multiplex (lysosomal storage diseases). Urine testing for mucopolysaccharides and oligosaccharides may uncover many of the large group of lysosomal storage disorders. Measuring plasma amino

acids and urine organic acids is a good screen for disorders in these groups.

Transferrin electrophoresis helps with CDG, which are N-linked glycan synthesis disorders. Peroxisomal disorders can be screened for by measuring very long-chain fatty acids and phytanic acid. A pH and lactate measurement may reveal longstanding acidosis and elevated lactate values. Ammonia concentrations may be elevated with enzyme deficiencies of the urea cycle or some organic acid disorders. An acylcarnitine profile, similar to tandem mass spectrometry testing for newborn screens, can assist in the detection of fatty acid oxidation defects, carnitine transport defects, amino acid disorders, and organic acid disorders.

Results of the initial assessment (history and physical examination) can help to guide the evaluation, and some of these tests may be omitted. Positive results from such testing may lead to additional investigation and confirmatory testing by either an enzyme assay or DNA testing.

EDITOR'S NOTE. The second part of this article, which is published in the online edition of this issue, is a comprehensive overview of specific inborn errors of metabolism. Most readers will use this material as a reference resource. All readers are urged to familiarize themselves with this second portion of the article, which reflects a prodigious effort on the part of Dr Levy.

PIR Quiz

Quiz also available online at pedsinreview.aappublications.org.

5. On the second day after birth, an initially vigorous term infant begins to feed poorly, develops tachypnea, and becomes increasingly less responsive to stimulation. No other abnormal findings are detected on physical examination. Chest radiograph appears normal. Laboratory evaluation reveals a normal complete blood count; differential count; pH; and serum electrolytes, glucose, and lactate. Serum ammonia concentrations are high and urine ketones are absent. Of the following, the *most* likely explanation is:

   A. Fatty acid oxidation defect.
   B. Organic acidemia.
   C. Renal tubular acidosis.
   D. Sepsis.
   E. Urea cycle defect.

6. On the second day after birth, an initially vigorous term infant begins to feed poorly, develops tachypnea, and becomes increasingly less responsive to stimulation. No other abnormal findings are detected on physical examination. Chest radiograph appears normal. The complete blood count and differential count are normal. The pH is low, serum ammonia value is high, sodium and chloride values are normal, potassium is elevated, bicarbonate is low, serum glucose is low, and serum lactate is slightly elevated. Ketones are present in the urine. Of the following, the *most* likely explanation is:

   A. Fatty acid oxidation defect.
   B. Organic acidemia.
   C. Renal tubular acidosis.
   D. Sepsis.
   E. Urea cycle defect.

7. A previously healthy 2-month-old girl rapidly becomes comatose shortly after the onset of an apparent upper respiratory tract infection. Aside from clear nasal discharge and coma, findings on her physical examination are unremarkable. Chest radiography appears normal. Laboratory findings include a normal complete blood count and differential count, pH, serum electrolytes, and serum lactate. Serum ammonia values are high and serum glucose is low. There are no ketones in the urine. Of the following, the *most* likely explanation is:

   A. Fatty acid oxidation defect.
   B. Organic acidemia.
   C. Renal tubular acidosis.
   D. Sepsis.
   E. Urea cycle defect.

8. A 12-month-old boy who has had progressive loss of developmental milestones over the past 6 months is found to have a cherry red spot on examination of each retina. He *most* likely suffers from a disorder of:

   A. Glycoprotein synthesis.
   B. Glycosylation.
   C. Lysosomes.
   D. Mitochondria.
   E. Peroxisomes.

9. Physical examination of a newborn reveals a high forehead, flat occiput, large anterior fontanelle, hypoplastic supraorbital ridges, epicanthal folds, and micrognathia. The infant *most* likely has a disorder of:

   A. Amino acid metabolism.
   B. Fatty acid oxidation.
   C. Glycogenolysis.
   D. Lysosomes.
   E. Peroxisomes.

Correction

In the article "Adolescent Immunizations" in the February 2009 issue (*Pediatr Rev.* 2009;30:47–56), in Table 1, "group B *Streptococcus* (GBS)" is in error. The correct phrase is "Guillain-Barré syndrome (GBS)" and applies to both places where "GBS" is printed in that table. In addition, on page 55 of the article, the last sentence in the first paragraph of the section headed "Polio" should read: "Poliovirus, a member of the enterovirus family, perhaps is best known for causing a rapid onset of asymmetric acute flaccid paralysis with areflexia."

Inborn Errors of Metabolism:
Part 2: Specific Disorders

Paul A. Levy, MD*

Author Disclosure
Dr Levy did not disclose any financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The following article is included online only as a second part of the article "Inborn Errors of Metabolism: Part 1."

Amino Acid Disorders

There is no one prototypical disorder of amino acid metabolism; each disorder has its own unique collection of symptoms. Four well-described amino acid disorders have been chosen as examples of this group.

Phenylketonuria, a disorder of phenylalanine metabolism, leads to intellectual disability if untreated.

Maple syrup urine disease involves an enzyme common to the degradation of the branched-chain amino acids (leucine, isoleucine, and valine). Although there are five subtypes of maple syrup urine disease, the classic form has a neonatal onset and generally progresses from poor feeding to coma and death if not treated.

Tyrosinemia also has multiple subtypes. Hepatorenal tyrosinemia (type I) may present with liver failure (elevated transaminase concentrations, hyperbilirubinemia, coagulopathy, ascites, and gastrointestinal bleeding) as well as kidney involvement (tubular dysfunction) and peripheral nerve involvement (painful crises, weakness or paralysis). Type II tyrosinemia is an oculocutaneous form of the disease that has corneal lesions and skin findings.

Homocystinuria, most commonly caused by cystathionine beta-synthase deficiency, presents with ocular (ectopia lentis), skeletal (marfanoid features such as dolichostenomelia and arachnodactyly), vascular (thromboembolic), and central nervous system (intellectual disability, stroke, and seizures) abnormalities.

When an amino acid disorder is suspected, measurement of plasma amino acids generally is sufficient to make the diagnosis. Assessment of urine amino acids can be helpful for homocystinuria and some abnormalities of amino acid transport (cystinuria, dicarboxylic amino aciduria) that affect the kidneys and for detecting generalized amino aciduria found with some kidney disease and mitochondrial disorders.

Urea Cycle Disorders

The degradation of amino acids results in their deamination, generating ammonia as the waste nitrogen. The urea cycle removes the excess ammonia by generating urea, which is eliminated in the urine. Six disorders of the urea cycle are known. Classic forms of urea cycle defects present in the first few days after birth with poor feeding, vomiting, tachypnea (sometimes with respiratory alkalosis), and lethargy that progresses to coma. There also are later-onset forms of many of the urea cycle disorders. Ornithine transcarbamylase (OTC) deficiency is an X-linked disorder, so it occurs more commonly in males, although carrier females may become symptomatic sometime during their lifetimes. Only

Abbreviations

ALD:	adrenoleukodystrophy
AMN:	adrenomyeloneuropathy
CACT:	carnitine acylcarnitine translocase
CNS:	central nervous system
CPK:	creatine phosphokinase
CPS:	carbamyl phosphate synthetase
CPT:	carnitine palmitoyltransferase
CSF:	cerebrospinal fluid
GSD:	glycogen storage disease
LCAD:	long-chain acyl-coA dehydrogenase
LCFA:	long-chain fatty acid
MCAD:	medium-chain acyl-coA dehydrogenase
MLD:	metachromatic leukodystrophy
MPS:	mucopolysaccharidosis
mtDNA:	mitochondrial DNA
NAGS:	N-acetyl glutamate synthetase
nDNA:	nuclear DNA
OTC:	ornithine transcarbamylase
OXPHOS:	oxidative phosphorylation
RCDP:	rhizomelic chondroplasia punctuate
SCAD:	short-chain acyl-coA dehydrogenase
VLCAD:	very long-chain acyl-coA dehydrogenase
VLCFA:	very long-chain fatty acids

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arginase deficiency, a defect of the last step of the urea cycle, does not present with the hyperammonemia common to the other urea cycle disorders. Instead, it presents with neurologic manifestations (progressive spastic quadriplegia, tremor, choreoathetosis, ataxia, seizures, and slowing of cognitive development).

The difficulty with diagnosing the urea cycle disorders is their lack of biochemical abnormality on routine testing; electrolytes and liver enzyme values usually are normal. Many infants who have urea cycle defects initially are believed to have sepsis. Only if ammonia is measured in a sick neonate can the suggestion of a defect in the urea cycle be seen. Assessment of plasma amino acid concentrations often makes the diagnosis. Determination of the orotic acid value may be necessary to distinguish between OTC or carbamyl phosphate synthetase (CPS) deficiency and the rarer N-acetyl glutamate synthetase (NAGS) deficiency (OTC deficiency causes an elevated orotic acid concentration, whereas CPS and NAGS deficiencies are associated with normal or low orotic acid values).

Organic Acid Disorders

This group of disorders results from enzyme deficiencies in pathways of amino acid degradation. Defects in the metabolism of the branched-chain amino acids (leucine, isoleucine, valine) as well as tyrosine, homocysteine, methionine, threonine, lysine, hydroxylysine, and tryptophan are responsible for most of the 25 organic acid disorders. Some of these conditions have been described in only a few patients. The distinction between organic acid disorders and amino acid disorders, however artificial, generally stems from how the disorders are detected. Amino acid disorders are diagnosed by high-performance liquid chromatography amino acid analysis and organic acid disorders by urine organic acid analysis, usually by gas chromatography mass spectrometry.

Many disorders in this group present with acidosis, due to the nature of the accumulating metabolite. Hypoglycemia, lactic acidosis, and ketosis also may occur, either separately or in combination. Analysis of urine for organic acids is the mainstay of diagnosis, and an acylcarnitine profile often is helpful. This test can be performed on blood spotted on newborn screening filter paper.

Carbohydrate Disorders

Glycogen Storage Diseases (GSDs)

These disorders can be subdivided into those that present primarily with liver disease, those that can affect muscle and liver, and those that primarily affect muscle. Because the disorders were numbered in the order of their discovery, the numbers are not useful in separating the disorders by clinical symptoms. GSD I, III, VI, and IX present with hepatomegaly and hypoglycemia. GSD III is subdivided into patients who have no muscle involvement (IIIb) and those who develop muscle weakness by their teenage years (IIIa). GSD IV leads to the formation of an abnormal glycogen that appears to be exceedingly noxious to the liver. Severe liver disease develops in the first few months after birth, leading to cirrhosis. Unlike the other primarily liver disorders, GSD IV often causes severe liver failure before the hypoglycemia is evident. GSD V, VII, and II primarily involve muscle. GSD II is unique in that it is a lysosomal storage disorder that presents in early childhood with progressive cardiomyopathy and hypotonia. GSD V and VII often present in adolescence with exercise intolerance and myoglobinuria.

Hypoglycemia and hepatomegaly suggest a GSD. Measuring concentrations of glucose, uric acid, lactic acid, liver transaminases, and lipids (cholesterol and triglycerides) generally is helpful. GSD I is distinguished from the other disorders that primarily affect liver by markedly elevated lactic acid as well as elevated uric acid and cholesterol concentrations. GSD III is characterized by normal or slightly increased concentrations of lactic acid, normal uric acid, but a greater elevation of triglycerides and cholesterol than GSD I. Creatinine phosphokinase (CPK) may be elevated in older children and adolescents if there is muscle involvement. GSD VI and IX have more benign courses than GSD I and III. Hypoglycemia is less severe, and hepatomegaly often resolves after puberty. Liver failure with portal hypertension suggests GSD IV. A liver biopsy usually is necessary to confirm the diagnosis of the liver GSDs, but DNA testing is increasingly available.

Myoglobinuria after exertion, with exercise intolerance that appears in adolescence, is highly suggestive of GSD V and VII. A muscle biopsy may be necessary to confirm the diagnosis. DNA testing now offers an alternative. DNA testing should help distinguish between type V and type VII.

Galactosemia

There are three disorders of galactose metabolism, but it is a deficiency of the second step of the pathway that is referred to as galactosemia. Infants who have classic galactosemia present with poor weight gain, poor feeding, vomiting, lethargy, jaundice, and hepatomegaly. They also are prone to sepsis from *Escherichia coli*. If the jaundice does not bring them to medical attention, it may resolve and the infants subsequently develop cirrho-

sis with portal hypertension and ascites. The diagnosis is confirmed by enzyme assay, usually on red blood cells

Hereditary Fructose Intolerance

The first exposure to fructose, usually from the disaccharide sucrose (fructose and glucose), results in vomiting and poor feeding. Continued exposure to fructose results in failure to thrive, hepatomegaly, hypoglycemia, jaundice, and renal dysfunction, followed by liver failure with clotting abnormalities, elevated liver transaminases, and ascites. Removal of fructose from the diet usually leads to rapid improvement, but this action requires suspicion of a problem with fructose. Elimination of other causes of hepatomegaly and hypoglycemia often suggest hereditary fructose intolerance. The diagnosis is confirmed by enzyme assay on a liver biopsy. DNA analysis is available for the common mutations.

Fructose-1,6-bisphosphatase Deficiency

Deficiency of this enzyme leads to hypoglycemia resulting from disruption of glucose production by gluconeogenesis. Hypoglycemia, lactic acidosis, and ketosis with hepatomegaly often are presenting signs. Generally, other disorders that cause both hypoglycemia and lactic acidosis need to be excluded. Improvement should be seen with removal of fructose from the diet. Confirmation is by enzyme assay on a liver biopsy.

Protein Glycosylation Disorders

This group of disorders is based on the relatively recent discovery of defects in protein glycosylation. As much as 50% of the body's proteins are modified with sugar (glycan) side chains. The glycan side chains modulate protein function, regulate protein half-life, provide structure (collagen and proteoglycans), and are involved in antibody recognition. Three types of linkage are used to modify proteins. N-linkage occurs with asparagine; O-linkage with serine, threonine, or hydroxylysine; and C-linkage with tryptophan. Defects with the formation of the N- and O-linkage have been reported, but not, as yet, for the C-linkage group.

N-linked glycosylation defects are referred to as congenital disorders of glycosylation. A characteristic of these disorders is the varied involvement of many organ systems. Intellectual disability, hypotonia, seizures, hepatic dysfunction, failure to thrive, vomiting, recurrent infections, and cerebellar hypoplasia are all features of this group.

O-linked glycoproteins are subdivided by the bridging sugar between the glycan side chain and the serine, threonine, or hydroxylysine amino acid in the protein. Bridging sugars include N-acetylgalactosamine, galactosamine (O-galactosyl glycans), xylose (O-xylosyl glycans), mannose (O-mannosyl glycans), and fucose (O-fucosyl glycans).

Two disorders associated with xylose as the bridging sugar include a progeroid variant of Ehlers-Danlos syndrome and a multiple exostosis syndrome. Mannose sometimes is a bridge for glycoproteins found in brain, muscle, and nerves. Walker-Warburg syndrome, muscle-eye-brain disease, a limb girdle muscular dystrophy, and several other congenital muscular dystrophies have been reported to have defects of O-linked glycosylation.

The N-linked disorders can be diagnosed by transferrin electrophoresis. This glycosylated protein found in blood helps to identify the N-linked glycosylation defect. Diagnosis of the O-linked disorders is more difficult, and transferrin testing is not helpful. For this mannose-bridged group, immunostaining of muscle biopsy specimens can look for dystroglycan abnormalities. Electrophoresis of apolipoprotein C-III is useful for diagnosing mucin type proteoglycans (those with N-acetylgalactosamine as a bridge).

Lysosomal Disorders

Lysosomes are cellular organelles that contain more than 30 acid hydrolases that degrade complex cellular molecules to their building blocks. A deficient enzyme results in the accumulation or storage of an intermediate compound. Over time, this stored material leads to cellular damage and disease symptoms. Three groups of lysosomal storage disorders are discussed, and all involve complex organic molecules called glycoproteins. These molecules have a protein backbone to which a polysaccharide side chain (glycan) is attached.

The first group of disorders has deficiencies of lysosomal enzymes that degrade the polysaccharide chain (glycosaminoglycan) and lead to the mucopolysaccharidoses (MPSs). The second group has deficiencies of the enzymes that degrade glycoproteins with a less complex polysaccharide than the glycan involved in the MPSs. Molecules that have this simpler polysaccharide are termed oligosaccharides. The oligosaccharidoses include mannosidosis, sialidosis, fucosidosis, and aspartylglucosaminuria. The third group is the sphingolipidoses. This group involves glycoproteins with a backbone comprised of sphingosine and a long-chain fatty acid (LCFA) to produce ceramide. These sphingolipidoses include Fabry, Farber, Gaucher, Krabbe, and Niemann-Pick diseases, as well as G_{M1} and G_{M2} gangliosidoses and metachromatic leukodystrophy (MLD).

Mucopolysaccharidoses (MPSs)

Children who have an MPS disorder are normal at birth. The disorders are progressive, with most having neurologic involvement that leads to characteristic regression and loss of milestones. Most affected patients have intellectual disability. Hepatosplenomegaly is found in most of the disorders. Bone involvement leads to short stature and the characteristic radiologic findings (dysostosis multiplex). Many children who have MPS disorders have frequent bouts of otitis media.

The seven MPS disorders include three that have both central nervous system (CNS) and somatic involvement (MPS I: Hunter/Scheie syndrome, MPS II: Hunter syndrome, and MPS VII: Sly syndrome), one disorder that has somatic involvement but minimal CNS involvement (MPS VI: Maroteaux-Lamy syndrome), one disorder that has CNS involvement and minimal somatic involvement (MPS III: Sanfilippo syndrome), and two disorders that have bone or joint involvement (MPS IV: Morquio syndrome and MPS IX).

Coarsened facial features, hepatosplenomegaly, joint involvement, and developmental delay followed by regression are presenting features in children who have an MPS. Radiographs looking for evidence of bony involvement (dysostosis multiplex) often are helpful. A screening test may bolster the suspicion if the glycosaminoglycans are increased in the urine, but the diagnosis generally is confirmed by enzyme assay.

Oligosaccharidoses

This group is similar to the MPSs, with many disorders associated with coarsened facial features, hepatosplenomegaly, and retinal (cherry red spot) or corneal involvement. Regression also is found with this group of lysosomal storage disorders.

Urine tested for glycosaminoglycans is negative, despite the concern for an MPS disorder. Urine for oligosaccharides may suggest one of the disorders in this group. Radiographs show dysostosis multiplex for many of the oligosaccharidoses. In addition, alpha mannosidosis should be considered in the presence of severe dysostosis multiplex, hepatosplenomegaly, and intellectual disability. Beta-mannosidosis may be distinguished by hearing loss, sialidosis by cherry red spots and myoclonus, and fucosidosis by recurrent respiratory infections and angiokeratoma (similar to Fabry disease). An enzyme assay is used to confirm the suspected diagnosis in most cases.

Sphingolipidoses

The prominent features of this group include hepatosplenomegaly (Niemann-Pick disease, G_{M1} gangliosidosis, Gaucher disease), demyelination (Krabbe disease, MLD, G_{M1} and G_{M2} gangliosidoses), and neuronal storage (G_{M1} and G_{M2} gangliosidoses). Most of these disorders are characterized by neurologic regression.

Initial normal development followed by neurologic regression suggests a lysosomal storage disorder. Although a negative test for glycosaminoglycans and oligosaccharides in urine does not completely rule out an MPS or oligosaccharidosis, this finding does suggest consideration of a sphingolipidosis (which does not have any abnormality of glycosaminoglycans or oligosaccharides). Magnetic resonance imaging may show demyelination, and an ophthalmologic examination may reveal a cherry red spot. Diagnosis and confirmation generally are by enzyme assay.

Peroxisomal Disorders

Peroxisomes are cellular organelles involved in beta-oxidation of very long-chain fatty acids (VLCFAs), the degradation of phytanic acid by alpha-oxidation, and the synthesis of plasmalogens. Peroxisomal disorders can be divided into two groups: peroxisomal biogenesis disorders, typified by Zellweger syndrome, and disorders involving mutations of individual peroxisomal enzymes.

Zellweger Syndrome Spectrum Group

Peroxisomal biogenesis disorders fall into a spectrum, with Zellweger syndrome being the most severe, infantile Refsum disease being less severe, and neonatal adrenoleukodystrophy (ALD) being somewhat milder. Zellweger syndrome is the prototypical biogenesis disorder. It is characterized by dysmorphic features (high forehead, flat occiput, large anterior fontanelle, hypoplastic superior orbital ridges, epicanthal folds, broad nasal bridge, anteverted nostrils, and micrognathia), brain defects (migrational brain defects with microgyria, pachygyria, and dysmyelination) and seizures, liver disease (dysfunction and cirrhosis), adrenal insufficiency, and often, renal abnormalities (microcysts). Children suffer severe intellectual disability (little, if any, development) and die from multiple problems, often in the first postnatal year.

Due to the biogenesis defect, all of the peroxisomal enzymes are deficient. Patients generally accumulate VLCFAs and develop abnormalities in phytanic acid (high) and plasmalogens (low).

Rhizomelic Chondrodysplasia Punctata (RCDP)

The peroxisomal biogenesis disorders are due to defects in the importation of proteins produced in the cytosol into the peroxisomes. Another peroxisomal biogenesis disorder, RCDP, is due to an importation defect of a subset of peroxisomal enzymes that use a different recognition marker. Most of the peroxisomal enzymes normally are imported, with only a few that use the different recognition marker failing to reach their place within the peroxisome. B-oxidation of LCFAs and VLCFAs is unaffected, but phytanic acid alpha oxidation and plasmalogen synthesis are affected. Clinical features of the three types of RCDP are similar, but type 1 is a peroxisomal biogenesis defect, while types 2 and 3 are single-enzyme defects of peroxisomal enzymes. Patients have rhizomelic shortening of the limbs (humerus more than femur), joint contractures, congenital cataracts, calcific stippling of epiphyses of long bones, growth failure, and profound developmental delay.

VLCFA concentrations are normal. Red blood cell plasmalogens are low, and phytanic acid concentrations are elevated. For types 2 and 3 RCDP, only the red blood cell plasmalogens are low; phytanic acid values are normal. Care should be taken not to draw conclusions about normal phytanic acid values because, with the diet as the only source of phytanic acid, concentrations in young patients may be normal, only becoming elevated over time. Enzyme assays on fibroblasts or DNA analysis may be necessary to distinguish the different types of RCDP.

Peroxisomal B-oxidation of LCFAs and VLCFAs

A few deficiencies of the enzymes involved in the B-oxidation of VLCFA have been described. They generally present similarly to the Zellweger spectrum disorders. One disorder even has been reported to have a neuronal migration defect similar to the Zellweger spectrum disorders, which suggests that this abnormality in the Zellweger spectrum may be due to abnormal B-oxidation of LCFA and VLCFA.

Another disorder of peroxisomal B-oxidation, racemase deficiency, presents with a late-onset neuropathy, rather than a picture similar to the Zellweger spectrum disorders.

X-linked ALD

This disorder is presumed to involve a peroxisomal membrane protein that transports VLCFA into the peroxisomes. Although not an enzyme defect of the VLCFA pathway, failure of such transport leads to accumulation of VLCFA (C22:0, C24:0). Two phenotypes have been described. The first is a childhood cerebral form that has an onset in the first decade after birth (mean age of 7 years) and has subtle initial manifestations of school behavioral problems (hyperactivity), emotional lability, and school failure. These initial features are followed by adrenal insufficiency and rapid progression of neurologic abnormalities believed to be due to an inflammatory reaction, with demyelination and gliosis of the parietal-occipital areas.

Adrenomyeloneuropathy (AMN) is a milder form of disease that presents with a later-onset, slowly progressive paraparesis (20s and 30s) that often is associated with adrenal insufficiency. AMN generally does not initially involve the brain, as does the childhood cerebral form of ALD, but 20% of affected patients eventually have brain abnormalities similar to those of childhood cerebral X-linked ALD. This group is referred to as AMN-cerebral.

Testing for elevation of VLCFA identifies patients who have defects of peroxisomal B-oxidation. Test results for other peroxisomal functions are normal. An enzyme assay on fibroblasts and DNA mutation analysis helps to separate the single-enzyme defects.

Plasmalogen Synthesis

Two enzyme defects of plasmalogen synthesis have been identified and present with a clinical picture similar to that of RCDP. In fact, the two defects are referred to as RCDP types 2 and 3. As with RCDP type 1, plasmalogen values are low, and this compound can be measured in red blood cells. Studies on skin fibroblasts often are necessary to distinguish the type of RCDP.

Peroxisomal Alpha-oxidation of Fatty Acids

Phytanic acid, a branched-chain fatty acid, whose only source is from dietary intake, undergoes alpha-oxidation in peroxisomes. Loss of this pathway results in accumulation of phytanic acid, which is the cause of Refsum disease (not infantile Refsum disease, which is a peroxisomal biogenesis disorder in the Zellweger spectrum). Clinically, Refsum disease is characterized by a tetrad of retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and increased cerebrospinal fluid (CSF) protein without increased cells. Symptoms usually are apparent before 20 years of age, with night blindness often being the first clinical symptom. Loss of the sense of smell and hearing loss also are common.

For patients who have Refsum disease, only phytanic acid concentrations are elevated. Although patients who have the Zellweger spectrum of disorders have elevated phytanic acid concentrations, VLCFA values also are abnormal.

Mitochondrial Fatty Acid Oxidation Defects and Carnitine Transport Defects

Mitochondrial Fatty Acid Oxidation Defects

Four enzymatic reactions are involved in the removal of 2-carbon fragments as acetyl-CoA from saturated fatty acids, which then are used for energy production. These steps are repeated in a spiral of B-oxidation that continues until only one 2-carbon fragment is left. Each of the four steps involved in B-oxidation of fatty acids has two or more enzymes that show specificity for different length fatty acids. The first step (acyl-CoA dehydrogenase) has four different enzymes, each with its own specificity. Short-chain acyl-CoA dehydrogenase (SCAD) shows specificity for fatty acids that are 4 to 6 carbons in length, medium-chain acyl-CoA dehydrogenase (MCAD) for those of 4 to 12 carbons, long-chain acyl-CoA dehydrogenase (LCAD) for those of 12 to 18 carbons, and very long-chain acyl-CoA dehydrogenase (VLCAD) for fatty acids 14 to 20 carbons in length. Disorders involving deficiencies of SCAD, MCAD, and VLCAD have been described, but patients who have deficiencies of LCAD have yet to be identified.

The third step has two known disorders and involves one of two 3-hydroxyacyl-CoA dehydrogenases. The first, short-chain 3-hydroxyacyl-CoA dehydrogenase, despite its name, acts on fatty acids of 4 to 16 carbons in length. The second, long-chain 3-hydroxyacyl-CoA dehydrogenase, favors the longer-chain fatty acids.

The unifying feature for disorders of mitochondrial fatty acid oxidation is the presence of hypoketotic hypoglycemia. SCAD, which catalyzes the last step and has C4 (butyl-CoA) as a substrate, may be the exception and rarely presents with hypoglycemia. Some of the enzyme deficiencies have a variant form, which produces myoglobinuria and muscle weakness. In general, if a fatty acid oxidation disorder is being considered, glucose concentration (both in the laboratory and by finger stick) should be measured, as well as concentrations of electrolytes, ammonia, liver transaminases, CPK, lactic acid, and uric acid. A complete blood count also should be obtained. Urine should be assessed for organic acids, and a routine urinalysis should be performed to help determine if there is myoglobinuria (positive blood on urinalysis but no red blood cells on microanalysis). An acylcarnitine profile can be helpful, as can assessment of urine for organic acids. A skin biopsy may be needed for enzyme analysis on fibroblasts to narrow down the actual enzymatic defect.

Carnitine Transport Defects

Carnitine helps to transport the longer-chain fatty acids (14 to 20 carbons in length) into mitochondria because unlike the medium-chain and short-chain fatty acids, they cannot pass through the mitochondrial membrane without assistance. Carnitine palmitoyltransferase I (CPT I) attaches carnitine to the fatty acid molecule, carnitine acylcarnitine translocase (CACT) transports the resulting molecule across the mitochondrial membrane, and finally, CPT II removes the carnitine and releases the fatty acid for B-oxidation.

Defects in the carnitine transport enzymes share some of the features of fatty acid oxidation defects, such as manifesting with hypoglycemia associated with hypoketosis, lethargy, and sometimes a Reye-like syndrome (hepatomegaly, elevated transaminases and ammonia). Seizures are not uncommon because of the hypoglycemia. The most common presentation of CPT II is an adult onset that involves muscle weakness, elevated CPK, and myoglobinuria after prolonged exertion.

If a carnitine transport defect is suspected, an acylcarnitine profile is a helpful initial test. CPT II and CACT have similar abnormalities that distinguish them from CPT I. In addition, CPT I may have normal-to-elevated carnitine concentrations. A skin biopsy with fibroblast studies may be necessary to distinguish between these disorders.

Mitochondrial Disease

Mitochondrial Disease Due to Mitochondrial DNA Alterations

As noted previously, mitochondria are involved in fatty acid oxidation (including carnitine transport). Mitochondria also have a role in the urea cycle, citric acid cycle, and most importantly, the energy production pathway of oxidative phosphorylation (OXPHOS). It is for defects in the energy-producing pathway, OXPHOS, that the term mitochondrial disease is reserved.

Mitochondria have their own DNA (mtDNA). The circular molecule encodes 37 proteins, including a translational system (2 ribosomal RNAs and 22 tRNAs) that differs from the cellular protein synthesis components and 13 OXPHOS proteins. The remaining (more than 70) OXPHOS proteins as well as nearly 900 proteins involved in other mitochondrial pathways are encoded by the nuclear DNA (nDNA). All mitochondria are derived from the ovum, so mtDNA disorders are maternally inherited. Mitochondrial disease due to nDNA mutations have been reported to have autosomal recessive, autosomal dominant, and X-linked inheritance patterns.

Mitochondria have multiple copies (3 to 10) of the mtDNA. Not all of the hundreds of mitochondria in the ovum are incorporated into the developing embryo. If incorporated into the embryo, the abnormal mitochondria may not be distributed equally to all tissues. The presence of different mtDNA molecules within a cell or individual is referred to as heteroplasmy. Energy production is affected by the presence of heteroplasmy within a mitochondrion. The mitochondria harboring mtDNA mutations generally are less able to produce energy. Clinical symptoms become apparent when the energy production is below the energy requirements of a particular tissue. Tissues that have high energy requirements, such as brain, liver, and kidney, are more susceptible to mitochondrial disease.

A number of mtDNA disorders have been described. Kearns-Sayre syndrome, Pearson syndrome, and chronic progressive external ophthalmoplegia (CPEO) have deletions or duplications of the mtDNA. MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke), MERRF (myoclonic epilepsy with ragged red fibers), NARP (neurogenic weakness, ataxia, and retinitis pigmentosa), MILS (maternally inherited Leigh syndrome), hypertrophic cardiomyopathy, mitochondrial myopathy, LHON (Leber hereditary optic neuropathy), and SNHL (nonsyndromic aminoglycoside-induced sensory neural hearing loss) have point mutations of the mtDNA.

Mitochondrial Disease (OXPHOS) Due to Nuclear DNA Mutations

Because most of the mitochondrial genes are coded by nDNA, it is not surprising that now more than 30 known OXPHOS disorders are due to nDNA mutations. Some of these disorders involve OXPHOS genes directly, some involve the importation of mitochondrial enzymes synthesized in the cytosol, and others affect mtDNA synthesis or importation of nucleotides or nucleotide synthesis.

Diagnostic Testing

Mitochondrial disease can affect many types of tissues. Brain, heart, liver, kidney, and pancreas involvement, as well as hearing loss and endocrine dysfunction have been reported. Often, muscle weakness, stroke, cardiomyopathy, hearing loss, or endocrine dysfunction suggests a mitochondrial disorder. In fact, the somewhat unrelated involvement of multiple tissues often adds mitochondrial disease to the differential diagnosis.

Screening with lactic acid cannot identify all patients who have mitochondrial disease because this is an inconsistent finding with the disorders. A markedly elevated lactate concentration, however, should raise concern about a mitochondrial disorder. Elevation of lactate often occurs after use of a tourniquet, but the elevation also can be caused by dehydration, seizure activity, or improper specimen handing.

Determination of a lactate-to-pyruvate ratio may be helpful; a ratio greater than 30 is indicative of an OXPHOS defect. CSF lactate and pyruvate values also are helpful for some patients.

A biopsy, generally of muscle, is the most definitive method for diagnosis. The specimen should be examined for ragged red fibers as well as accumulation of mitochondria in the subsarcolemma layer of the muscle. Staining for succinate dehydrogenase and cytochrome C oxidase should be performed. Electron microscopy may show abnormal mitochondria or crystalline inclusions. A muscle specimen should be sent to a specialized laboratory for enzyme analysis of the OXPHOS pathway.