

Illustrated Baby Nelson

Special Pediatrics

By

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جعلہ اللہ صدقہ جاریہ لی ولوالدی ولذریعتی.
رفعه د. ماجد المنصور. دعواتکم

الدفعه ال14

Foreword

*I was very blessed to issue this new edition of Illustrated Baby Nelson with three pioneer figures in pediatrics and neonatology sharing their thoughts, insights and relentless revision of neonatology, hematology and pulmonology chapters. Hats off to **Dr Ayman Azab, Dr Osama Taha Amer, Dr Laila Sherief**.*

*Thank you for the man for whom I myself and this book owe him so much and without his support it would never come to light and persist; **Mr Sayed Mahmoud**, founder of university book center. Thanks to his soul that exist with and inspire us all*

And finally I end my foreword with these lines to Richard Templer:

"Be prepared to be a little brave every day. If you don't, you'll grow stagnant and mouldy. We all have a comfort zone where we feel safe and warm and dry. But every now and then we need to step outside and be challenged, be frightened, be stimulated. It's this way that we stay young and feel good about ourselves "

Richard Templer (The rules of life)

Mohamed El Koumi

October 6 city

7th of March 2017

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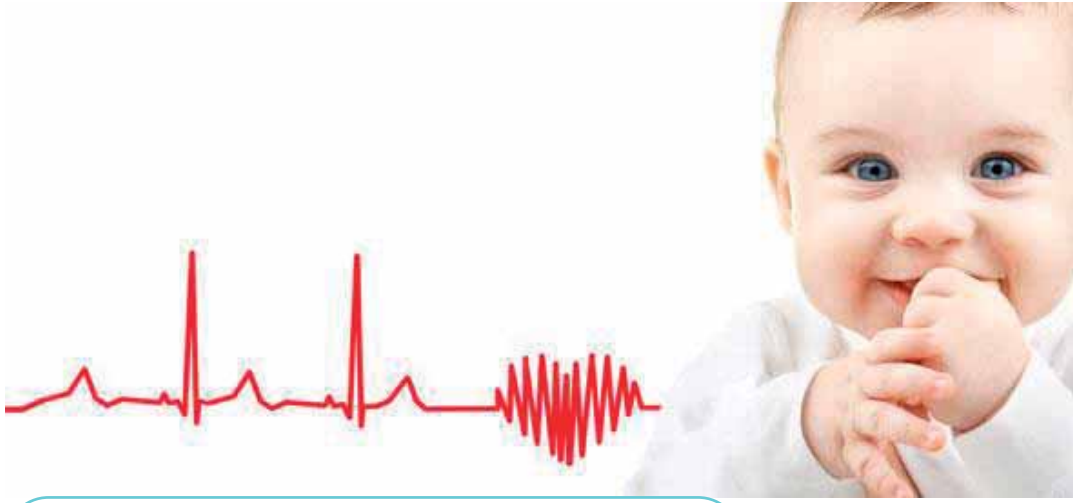
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Cardiology

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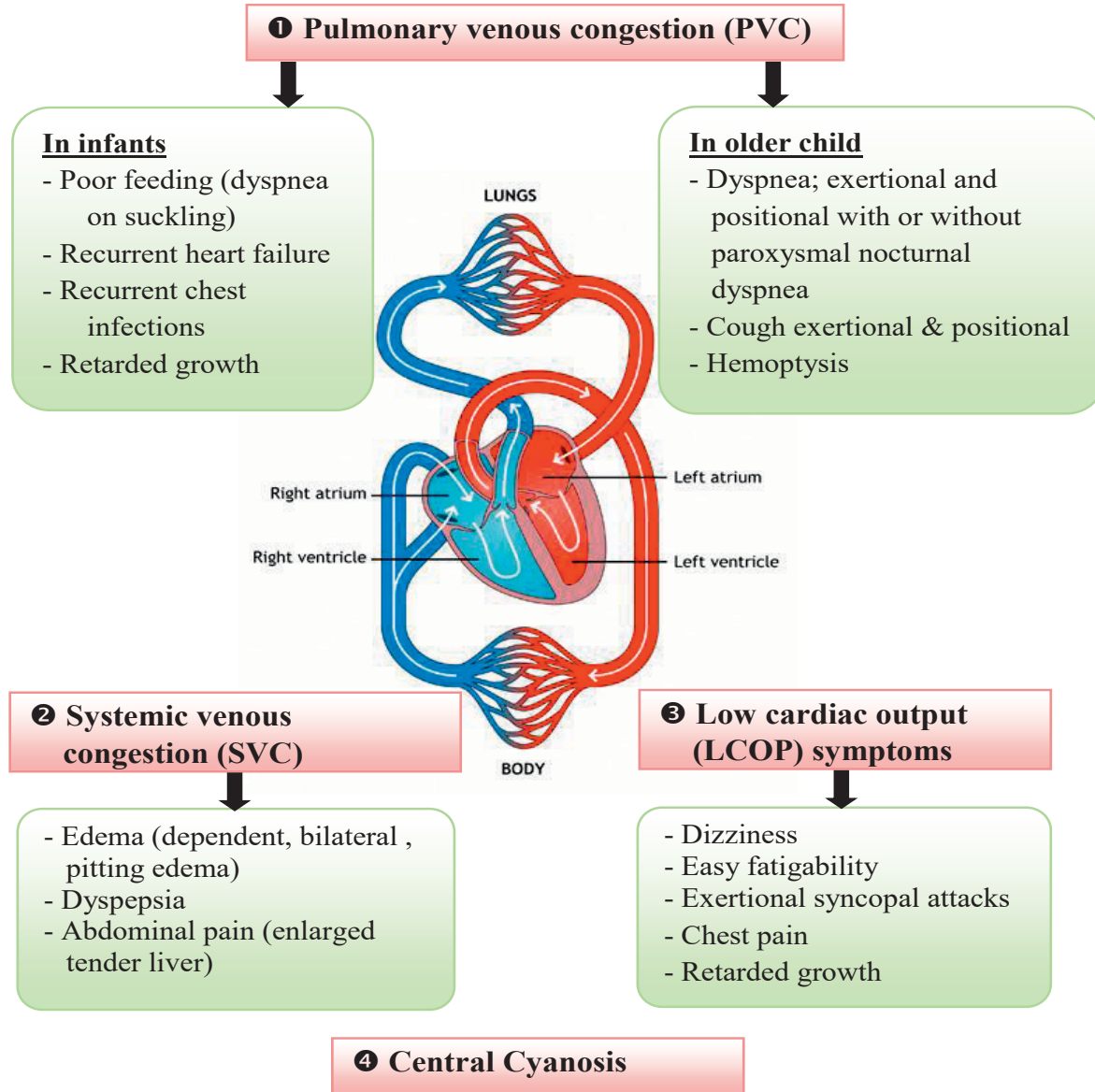
List Of Abbreviations

Lt. V.	: Left ventricle
Rt. V.	: Right ventricle
Lt. A	: Left atrium
Rt. A	: Right atrium
LVH	: Left ventricle hypertrophy.
RVH	: Right ventricle hypertrophy
LAD	: Left atrium dilatation
RAD	: Right atrium dilatation
C.P. angle.	: Cardiophernic angle
P.H⁺	: Pulmonary hypertension
S₁	: First heart sound
S₂	: Second heart sound
P₂	: Pulmonary component of the second heart sound
A₂	: Aortic component of the second heart sound.
RVF	: Right ventricle failure.
LVF	: Left ventricle failure
BVF	: Biventricular failure
COP	: Cardiac output
LPSB	: Left parasternal border
CXR	: Chest X-ray
SBE	: Subacute bacterial endocarditis
RBBB	: Right bundle branch block
VMA	: Vallinyle mandilic acid
BVH	: Biventricular hypertrophy.
PGE1	: Prostaglandin E1
PFO	: Patent formen ovale.
TOF	: Tetralogy of Fallot
DORV	: Double outlet right ventricle

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Diagnosis of a cardiac patient

Step 1: History Of

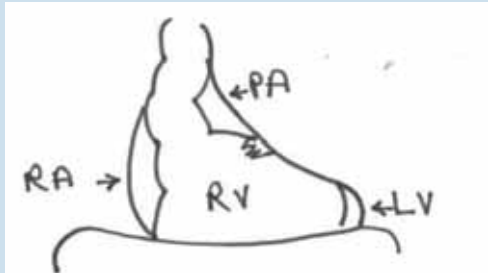

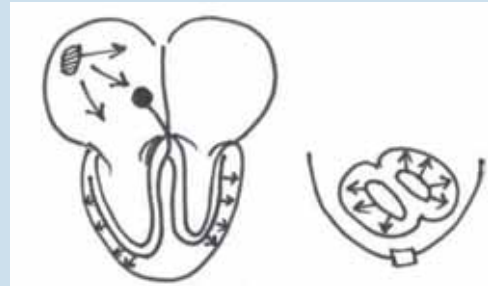
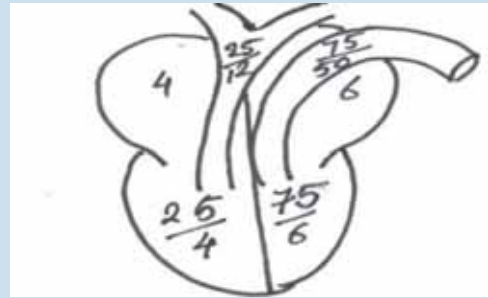


Step 2 : General examination for

Suspected congenital heart disease	Suspected rheumatic heart disease
<ul style="list-style-type: none"> - Cyanosis (in lips & extremities) - Characteristic facies (e.g. Down) - Check patient's weight and height And plot on appropriate charts - Check blood pressure & pulse - Clubbing of fingers and toes 	<ul style="list-style-type: none"> - Start with measuring blood pressure & checking peripheral signs suggesting AR. - Check for edema in dyspneic patient - Clubbing of fingers and toes and other features suggesting infective endocarditis

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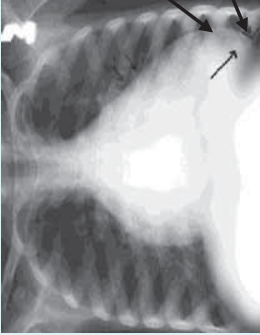
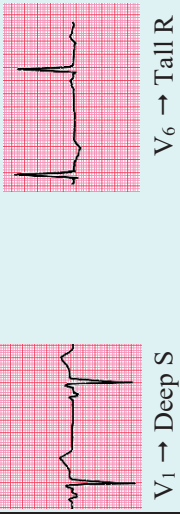
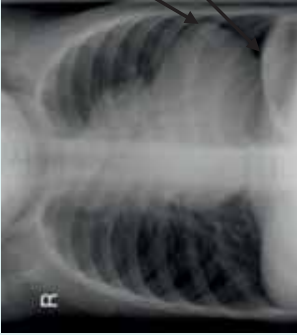
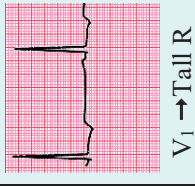
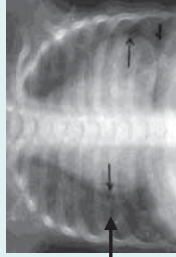

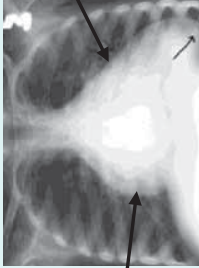

Remember the following notes

<p>A</p> <ul style="list-style-type: none"> * Most of the anterior surface of the precordium is made of right ventricle * Left atrium does not appear in anterior view * Any chamber enlarges in its longitudinal axis mainly 	 <p>A hand-drawn diagram of the heart in a frontal view. The right atrium (RA) is on the left, the right ventricle (RV) is in the center, the pulmonary artery (PA) is at the top, and the left ventricle (LV) is on the right. Arrows point to each chamber.</p>
<p>B</p> <p>During systole; left ventricle elongate to hit a localized area of chest wall producing the apex beat</p>	 <p>A hand-drawn diagram of the heart in a frontal view, showing the left ventricle elongated and hitting the chest wall, illustrating the apex beat.</p>
<p>C</p> <ul style="list-style-type: none"> * Right atrium depolarizes first followed by left atrium * Both ventricles depolarize at the same time * Ventricles depolarize from inwards to outwards 	 <p>A hand-drawn diagram of the heart in a frontal view, showing the sequence of depolarization. Arrows indicate the path of electrical activity from the SA node through the atria and into the ventricles.</p>
<p>D</p> <ul style="list-style-type: none"> * Pressures in the left side exceed that in the right * After birth pressures in the Right side are slightly higher than normal * Pressure values increase steadily with age 	 <p>A hand-drawn diagram of the heart in a frontal view, showing pressure values for different chambers. The values are: RA 4, RV 25/12, PA 75/50, LV 75/6, and aortic 120/80.</p>

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Step 3 : Precordial examination

Precordial examination includes inspection, palpation and percussion of the precordium. It detects basically cardiac chamber and or big artery enlargement

	Precordial examination	Chest X Ray	ECG
Left ventricle hypertrophy (LVH) or Enlargement	<ul style="list-style-type: none"> - Apex beat is shifted down and out - Apex beat is localized 	 <p>Apex shifts down & out Obtuse cardiophrenic angle</p>	 <p>V₁ → Deep S V₆ → Tall R</p>
Right ventricle hypertrophy (RVH) or Enlargement	<ul style="list-style-type: none"> - Apex beat is shifted directly out - Apex beat is diffuse - Precordial bulge - Left para sternal pulsation - Epigastric pulsation 	 <p>Apex shifts direct out Acute cardiophrenic Angle</p>	 <p>V₁ → Tall R V₆ → Deep S</p>
Right atrial dilatation (RAD)	Usually is not detectable clinically	 <p>↑ Right cardiac shadow</p>	<p>Tall, peaked P wave (P-pulmonale)</p> 
Left atrial dilatation (LAD)	Usually is not detectable clinically	 <p>Double contour Mitralization</p>	<p>wide and bifid P wave (P-mitrale)</p> 

Evidence of pulmonary artery dilatation in cases with pulmonary hypertension(PH)

- Palpation of the pulmonary area: Pulsating pulmonary area (normally silent area)
- Percussion of the pulmonary area: Dull (normally resonant area)

Feel the murmur i.e. Thrills (Thrill is a palpable murmur)Value of detecting thrill

- Definitely, there will be a murmur to be heard with the same timing of the thrill
- This murmur is organic never functional or innocent
- If the murmur is propagating ; the thrill usually is not propagating (i.e. localizing sign)

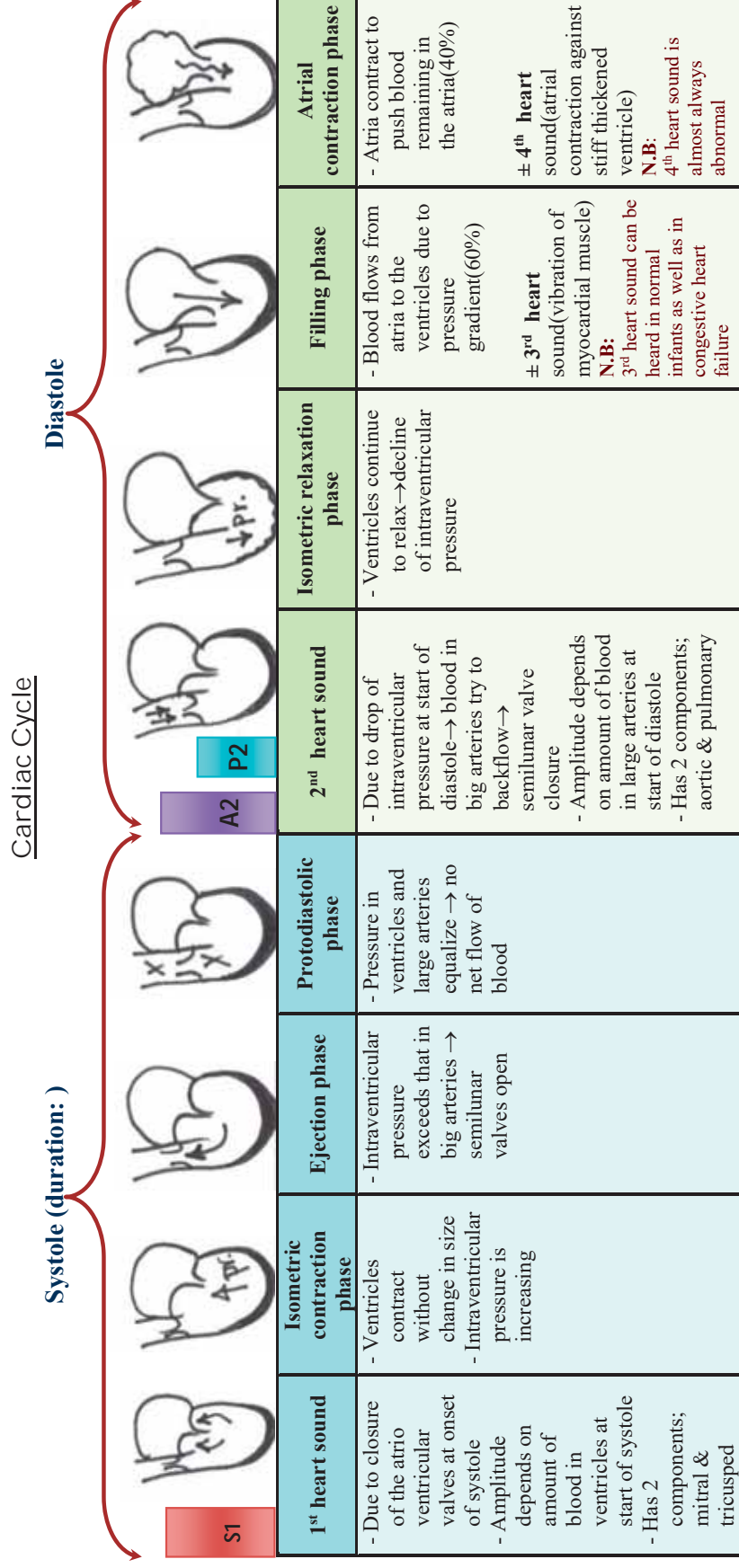
If thrill is detected; check where?

- Mitral area (left 5th interspace)
- Left parasternal border area(left 3rd and 4th interspaces)
- Pulmonary area(left 2nd interspace)
- Aortic area(right 2nd interspace)

**Comment on the apex with (Remember SCART)**

	Normal apex	Abnormal apex
Site	Occupies the left 5 th interspace, midclavicular line	<ul style="list-style-type: none"> - Shifted outward & downward (LVH) - Shifted direct outward (RVH) - Absent; impalpable
Character	Normal intensity	<ul style="list-style-type: none"> - Hyperdynamic (strong and rapid)in volume overload e.g. MR, CM,AR - Heaving(strong and sustained) in pressure overload e.g. AS
Area	Occupies one interspace	- Diffuse (apex beat occupies more than one interspace) in RVH
Rhythm	Regular	- Irregular in irregular arrhythmias
Thrills	Absent	<ul style="list-style-type: none"> - May be Present: <ul style="list-style-type: none"> o Systolic thrill (MR, CM, VSD) o Diastolic thrill (MS, CM)

MR: Mitral Regurge; CM: combined mitral lesion (previously double mitral);AR: Aortic Regurge; AS: Aortic stenosis; VSD: ventricular septal defect; MS: Mitral stenosis

**Q1: What is murmur?**

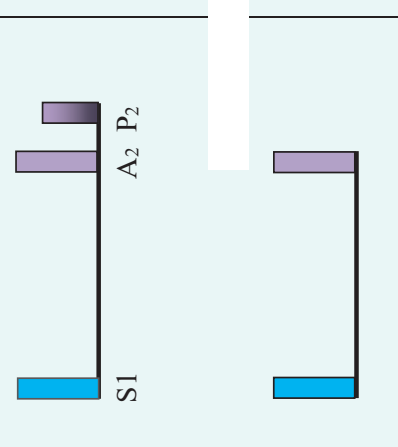
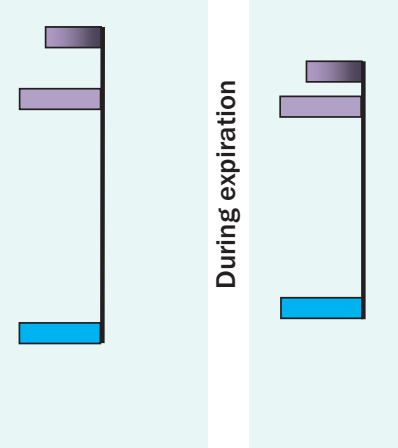
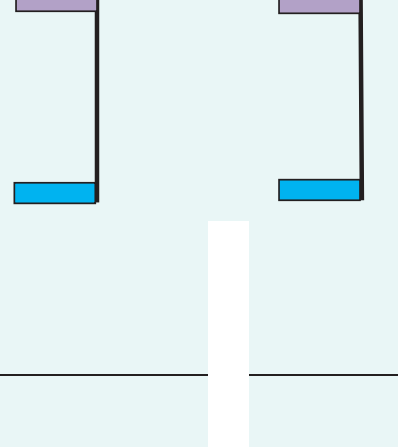
- It is abnormal sound due to either blood flowing in an abnormal direction **or** blood flowing across narrow orifice (organic narrowing e.g. stenosis **or** relative)
- Pressure gradient is required for murmur to develop
- Murmurs are graded into 6 grades according to intensity and presence or absence of associated thrills (Grades 1-3 are without thrill and grades 4 - 6 with thrill)
- Murmurs may be:
 1. Organic: due to organic lesion in the heart either congenital or acquired
 2. Relative: due to ↑ blood flow through normal sized valve (soft, non propagating, without thrills and heart sound related is usually accentuated e.g. relative PS in PH)
 3. Innocent murmur: heard over completely normal heart or great vessels. (soft, non propagating, without thrills, *systolic, asymptomatic patient, normal heart sounds*)

Step 4 : Auscultation







1. Heart sounds

1. First heart sound (S1)	2. Second heart sound (S2)
<ul style="list-style-type: none"> Due to closure of Atrio ventricular valves at beginning of systole Has 2 components → Mitral : best heard over mitral area → Tricuspid : best heard over tricuspid area Muffled in → Atrio ventricular valves regurge → Bradycardia Accentuated in → Atrio ventricular valves stenosis → Tachycardia S1 Splits in right and left Bundle branch block (BBB) 	<ul style="list-style-type: none"> Due to closure of semilunar valves at beginning of diastole Has 2 components → Aortic ; best heard over aortic area → Pulmonary ; best heard over pulmonary area Muffled in : semilunar valve stenosis: → Aortic stenosis (↓A₂) → Pulmonary stenosis (↓P₂) Accentuated in hypertension → Systemic hypertension (↑A₂) → Pulmonary hypertension (↑P₂) S2 Split : see below

Splitting of the second heart sound (Detected by auscultating the pulmonary area)

Physiologic splitting	Wide variable splitting	Wide fixed splitting
<p>The two components of S2(A₂: aortic component & P₂:pulmonary component) usually splits in inspiration & unites in expiration</p> 	<p>Wide variable splitting</p> <ul style="list-style-type: none"> S2 splits in whole respiratory cycle but wider splitting in inspiration Occur with prolonged or delayed right ventricular systole 	<p>Wide fixed splitting</p> <ul style="list-style-type: none"> Wide splitting Does not vary with the respiratory cycle Occurs with ASD 

2. Murmurs

1. Timing	Systolic Murmurs				Diastolic Murmurs	
	Pan systolic		Ejection systolic		Early diastolic	Mid diastolic
2. Site of maximum Intensity						
	Mitral area	Left sternal Border(3,4)	Tricusped area	Aortic area	Pulmonary area	Mitral area
Diagnosis	MR	VSD,ECD	TR	AS	PS	MS
Sounds	↓ S1		↓ S1	↓ A2	↓ P2	↑ S1
Characters	Blowing	Harsh	Blowing	Harsh	Harsh	Rumbling
Propagation	Axilla	Precordium		Neck& Apex	Sternal border	Localized

ECD: Endocardial cushion defect; TR: tricuspid regurge; PS: pulmonary stenosis

N.B: Continuous (machinery or systolic/diastolic) murmurs: See later in PDA

Q2: Auscultatory findings in pulmonary hypertension(PH)?

1. Ejection systolic murmur over pulmonary area (with the relative murmur criteria)
2. Accentuated pulmonary component of the second heart sound

N.B: pulmonary hypertension occur in cases with prolonged pulmonary congestion or prolonged increase pulmonary blood flow

Step 5 : Investigations

1. ECG and chest x ray: Help precordial examination in detecting cardiomegaly (ECG is invaluable for diagnosis of dysrhythmia and ischemia)

2. Echocardiography (& preoperative catheterization): **Help auscultation establishing the final diagnosis**

Value: - Describe lesions (site, size, intracardiac pressures, flow across the lesion and ventricular function).

- Detect complications e.g. Infective endocarditis, cardiomegaly

Congenital Heart Diseases (CHD)

Incidence

- 8 per 1000 live born infants have significant cardiac malformation
- The commonest CHD are VSD (30%), PDA (12%), and ASD (7%)
- About 10-15 % have complex lesions with more than one cardiac abnormality

Risk Factors

- Genetic predisposition suggested by family history of CHD
- Exposures during pregnancy e.g.
 - a. Drugs e.g. warfarin, anticonvulsants, alcohol
 - b. Diseases e.g. maternal rubella (→ PDA), Maternal Diabetes Mellitus
- Chromosomal e.g.
 - a. Down syndrome → Atrio ventricular septal defect, VSD
 - b. Turner syndrome → Aortic stenosis, coarctation of aorta
 - c. Williams syndrome → Supra valvular aortic stenosis , pulmonary stenosis



a



b



c

Presentation

- Coincidental; accidental discovery of a murmur in an asymptomatic infant
- Cardiac failure /Cardiogenic shock e.g. in neonate (critical aortic stenosis and severe coarctation) or in infants(CHD with high pulmonary flow)
- Congestive pulmonary symptoms e.g. CHD with high pulmonary flow
- Cyanosis e.g. congenital cyanotic heart diseases
- Cardiomegaly detectable clinically or during routine chest radiograph
- Certain anatomic diagnosis may not be made by physical examination or chest x ray or ECG alone ,so echocardiography is the mainstay of diagnostic imaging
- **Recently**
 1. Antenatal fetal anomaly ultrasound screening
 - Can diagnose up to 70 % of significant lesions ,allowing earlier diagnosis and planning of management
 - Important for any fetus with an increased risk e.g. Down syndrome
 2. MRI allows 3 dimensional imaging of complex CHD, assessment of hemodynamics, assists interventional cardiology and reduces the need for cardiac catheterization.

(Illustrated textbook of Paediatrics, Tom Lissauer)

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Acyanotic Congenital Heart Diseases (ACHD)

ACHD constitutes 80% of all CHD

Classification

i. ACHD with left to right shunt (Potentially cyanotic CHD)

The commonest lesions in this category are

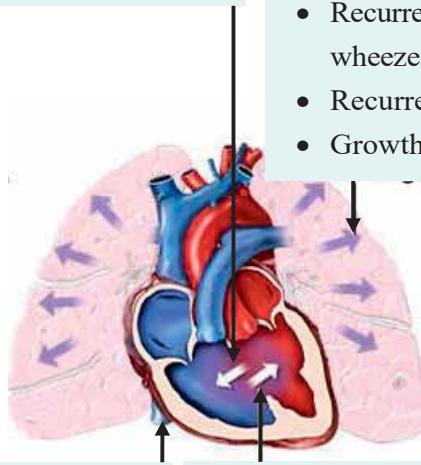
- Ventricular septal defect (VSD)
- Patent ductus arteriosus (PDA)
- Atrial septal defect (ASD)

General clinical features

- 1. Degree of the left to right shunt, and consequently clinical manifestations is dependent on:**
 - Size of the defect.
 - Pressure gradient across the defect.

2. Manifestations of high pulmonary blood flow

- Poor feeding (sweating and tachypnea) in babies, exercise intolerance and easy fatigability in children
- Recurrent chest infections & chest wheezes.
- Recurrent heart failure.
- Growth failure (faltering of growth)



3. Heart failure

Usually doesn't occur in full term neonates but can occur in infancy as pulmonary vascular pressure declines.

- 4. Eisenmenger syndrome:** Prolonged high pulmonary blood flow → pulmonary hypertension develops → with time, right side heart pressures exceeds that of the left → reversal of the shunt → central cyanosis
Risk is higher with large unrepaired defects

ii. ACHD without shunt

1. Obstructive lesions e.g. Aortic coarctation, Aortic stenosis, Pulmonary stenosis

Common clinical features:

- 1- Severe obstructive lesions can present early in life with heart failure.
- 2- Low cardiac output manifestations.

2. Non obstructive lesions e.g. Dextrocardia, Mitral valve prolapse

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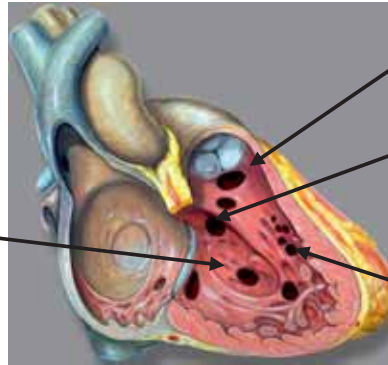
Ventricular septal defect (VSD)

Definition

Defect anywhere in the interventricular septum

Types of VSDs:

Perimembranous defect:
Adjacent to tricuspid valve
The commonest type (70%)



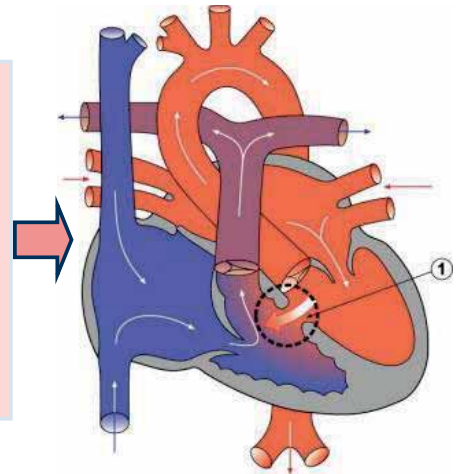
Inlet defect

Outlet defect; (also called infundibular or sub arterial).


Muscular defects: Either single or multiple (Swiss cheese).

Hemodynamics

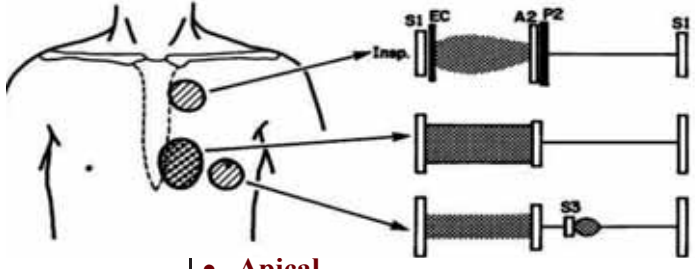
- Blood is shunted from the left ventricle (higher pressure) to the right ventricle (lower pressure)
- ↓
- Increased pulmonary blood flow
- ↓
- Pulmonary congestive symptoms.
- Volume overload over right ventricle, left atrium and left ventricle



Clinical picture

	Small VSD	Large VSD
General manifestations	<ul style="list-style-type: none"> - Usually asymptomatic - Discovered accidentally 	<p><u>History</u></p> <ul style="list-style-type: none"> • Breathlessness during suckling • Recurrent chest infections • Recurrent chest wheezes <p><u>Physical</u></p> <ul style="list-style-type: none"> • Breathlessness, tachypnea, tachycardia and enlarged tender liver (heart failure) • Faltering of growth
		

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	Small VSD	Large VSD
Precordial Examination	- Systolic thrill over the lower left sternal border	- Biventricular enlargement by 2 months of age - Active precordium
Auscultation	<ul style="list-style-type: none"> • <u>Murmur of VSD</u> <ul style="list-style-type: none"> - Pansystolic. - On lower left sternal border. - Propagate all over the heart. - Harsh ; <u>loud</u> . 	<ul style="list-style-type: none"> • <u>Murmur of VSD</u> <ul style="list-style-type: none"> Same <u>but</u> softer • <u>Pulmonary area</u>: Accentuated P₂ & soft systolic murmur indicates pulmonary hypertension.
		
		<ul style="list-style-type: none"> • <u>Apical</u> <ul style="list-style-type: none"> - Short rumbling mid diastolic murmur - Produced by the increased volume of blood flow across the mitral valve - Usually indicates a Pulmonary-to-systemic blood flow ratio of at least 2 : 1
Complications	• Infective endocarditis	<ul style="list-style-type: none"> • Heart failure • Infective endocarditis • Higher risk of Eisenmenger syndrome
Investigations		
*Chest X-ray	- Normal	- Cardiomegaly with biventricular enlargement & plethoric lungs.
* ECG	- Normal	- Biventricular enlargement (LVH and RVH)
* Echo	- Diagnostic (size smaller than aortic in diameter ;up to 3mm)	- Diagnostic
* Catheter	-	- Pre operative / interventional

Treatment

1. Small defect

- Avoid infective endocarditis by dental hygiene and antibiotic prophylaxis.
- Reassurance ; (surgical intervention is not usually recommended)
- Follow up with ECG & Echo to confirm spontaneous closure

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2. Large defect

A. Medical

- Control heart failure (Diuretics, Captopril).
- Antibiotics for chest infections
- Additional calorie input and monitor growth
- Avoid infective endocarditis
- Follow up with ECG & Echo to confirm spontaneous closure.

B. Surgical

⊕ Types

- i- Palliative: Pulmonary artery banding → reduce pulmonary blood flow
- ii- Direct closure of the defect

⊕ Indications

- i- Symptomatic large defects with uncontrollable heart failure or Growth failure
- ii- Progressive pulmonary hypertension.

⊕ Timing: at 3-6 months of life.

(Illustrated textbook of Paediatrics, Tom Lissauer)

Prognosis

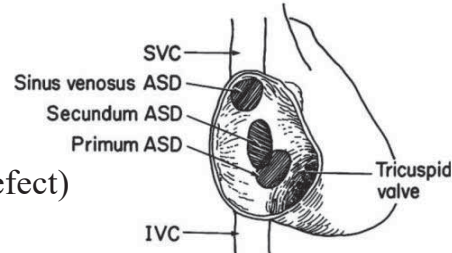
30-50% of small defects (especially muscular) close spontaneously within the first 2-years of life

Atrial Septal Defect (ASD)

Definition: Defect in the inter-atrial septum.

Types of ASD

- Secundum ASD
- Primum ASD (Partial atrio ventricular septal defect)
- Sinus venosus defect:
 - Lies in the upper part of the septum near orifice of superior vena cava.
 - Association: usually with partial anomalous pulmonary venous return



Secundum ASD	Primum ASD
<ul style="list-style-type: none"> • The commonest type (80% of ASD) • Lies in the middle part of the septum • <u>Association</u> May be with Holt Oram syndrome (Absent radii, 1st degree heart block, secundum ASD). 	<ul style="list-style-type: none"> • Less common • Lies in the lower part of the septum • <u>Association</u> Usually associated with cleft of mitral valve leaflet → mitral regurge.

Hemodynamics

Blood is shunted from left atrium to right atrium → right ventricle → ↑ pulmonary blood flow (more with primum ASD)

General manifestations

- | | |
|---|---|
| <ul style="list-style-type: none"> • Asymptomatic in most cases unless large ASD → features of increased pulmonary blood flow • Arrhythmias (4th decade onwards) | <ul style="list-style-type: none"> • Features of increased pulmonary blood flow in infancy including recurrent chest infections & heart failure. |
|---|---|

Precordial Examination

- | | |
|-------------------------------|-------------------------|
| - Usually normal (may be RVH) | - Cardiomegaly with BVH |
|-------------------------------|-------------------------|

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Auscultation

Pulmonary area

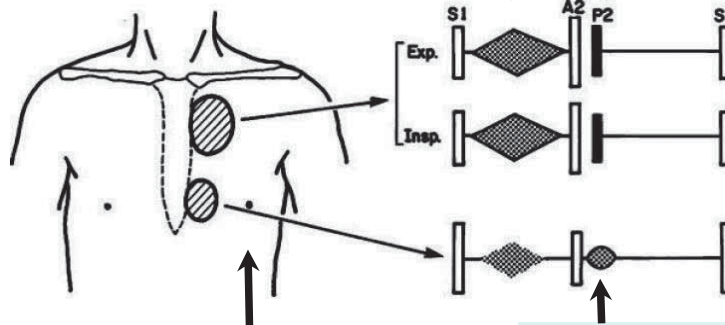
Murmur of a relative pulmonary stenosis:

- Soft ejection systolic without thrill
- With accentuated P2

Pulmonary area

Wide fixed splitting of S2:

- Wide splitting due to large filling of right ventricle
- Fixed (does not vary with respiration) due to constant filling of right ventricle in all phases of respiration



Apex

Pansystolic murmur of mitral regurg propagating to axilla in Primum ASD

Lower left sternal border

- A short, rumbling mid-diastolic murmur Produced by the increased volume of blood flow across the tricuspid valve
- Usually indicates a Pulmonary-to-systemic blood flow ratio ($Q_p : Q_s$) ratio of at least 2 : 1

Complications

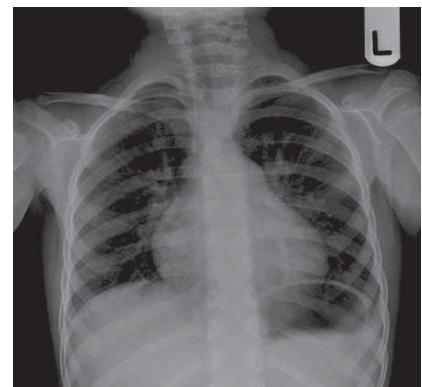
Very rare; more common with primum ASD:

- Recurrent heart failure may occur with large defects.
- Recurrent pulmonary infections
- Infective endocarditis is extremely rare (can occur in primum defects)
- Reversal of the shunt may occur very late; in adulthood, by the 3rd - 4th decade.

Investigations

1. Chest X-ray

- Cardiomegaly with RVH & RAD.
- BVH in ostium primum defect
- Plethoric lungs (\uparrow pulmonary vascular markings)



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2. ECG:

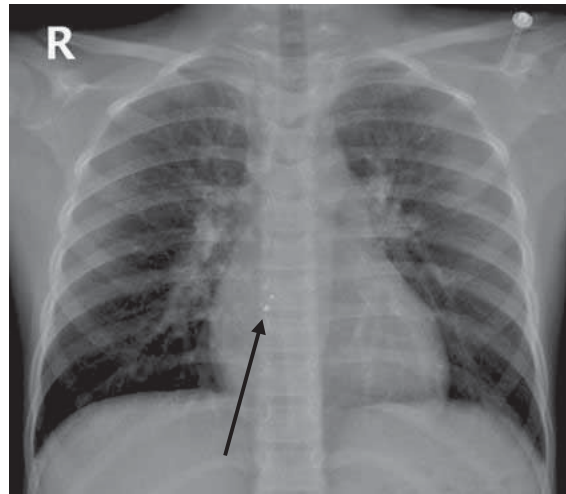
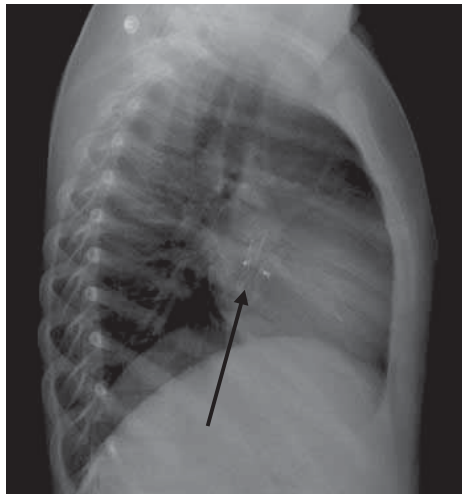
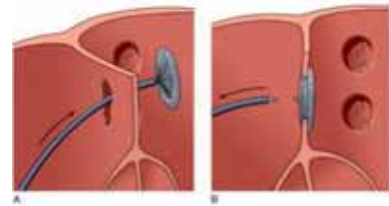
- RVH & RAD.(BVH in primum ASD)
- Right bundle branch block is common.

3. Echocardiography is diagnostic**4. Cardiac catheter:** - Pre operative/corrective intervention**Treatment****1. Medical**

- Same lines as for VSD
- Infective endocarditis prophylaxis is needed only for primum ASD with mitral regurge

2. Surgical or transcatheter device closure is advised for

- All symptomatic patients
- Asymptomatic patients with a Qp : Qs ratio of at least 2 : 1
- Those with right ventricular enlargement



(Chest x ray after ASD device closure, source: Radiopaedia.com)

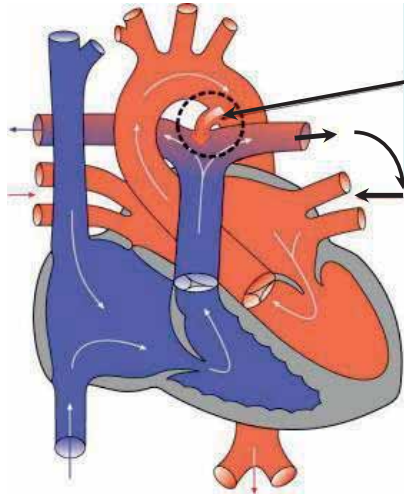
Prognosis

40% of secundum ASD defects close in 1st four years of life spontaneously

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Patent ductus arteriosus (PDA)

Definition: Persistent fetal duct connecting the aorta & the pulmonary artery.



Connections

- The aortic end is just distal to left subclavian artery.
- Pulmonary end is at the bifurcation.

Association: Congenital rubella syndrome & prematures

Hemodynamics

- Blood is shunted from the higher pressure of aorta to pulmonary artery → ↑↑ Pulmonary blood flow
- Run off of blood from Aorta to the pulmonary artery mainly during diastole → lower diastolic pressure → Hyperdynamic circulation

General Manifestations

1. Small duct

- Asymptomatic ; discovered accidentally

Precordial examination

- Systolic thrill over the upper left sternal border

2. Big duct

- Symptoms of increased pulmonary blood flow (see before)
- Hyperdynamic circulation e.g. big pulse pressure

Precordial examination

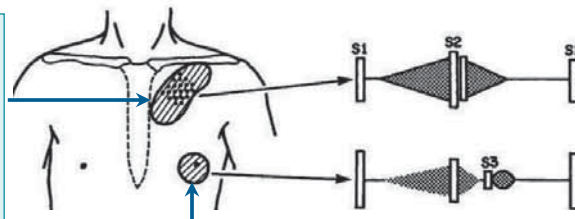
- Systolic thrill over the upper left sternal border
- Evidence of LVH

Auscultation

Left infraclavicular area

Continuous; machinery murmur (Gibson murmur); Murmur may be systolic if the diastolic component is masked:

1. Early in life (due to physiologically raised pulmonary pressure)
2. Very large defects (due to higher pulmonary pressure)
3. Pulmonary hypertension



Apex

- A short, rumbling mid-diastolic murmur
- Produced by the increased volume of blood flow across the mitral valve in big defects

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Investigations

1. Chest X ray and ECG

- Small /asymptomatic PDA→ Both are normal
- Large and symptomatic PDA → Indistinguishable from large VSD
 - Chest X-ray: Cardiomegaly and Plethoric lungs.
 - ECG: → Left ventricle hypertrophy with large left to right shunt
→ Right ventricle hypertrophy with pulmonary hypertension

2. Echocardiography is readily diagnostic

Complications

- As in large VSD plus Aneurismal dilatation and rupture of the duct

Treatment

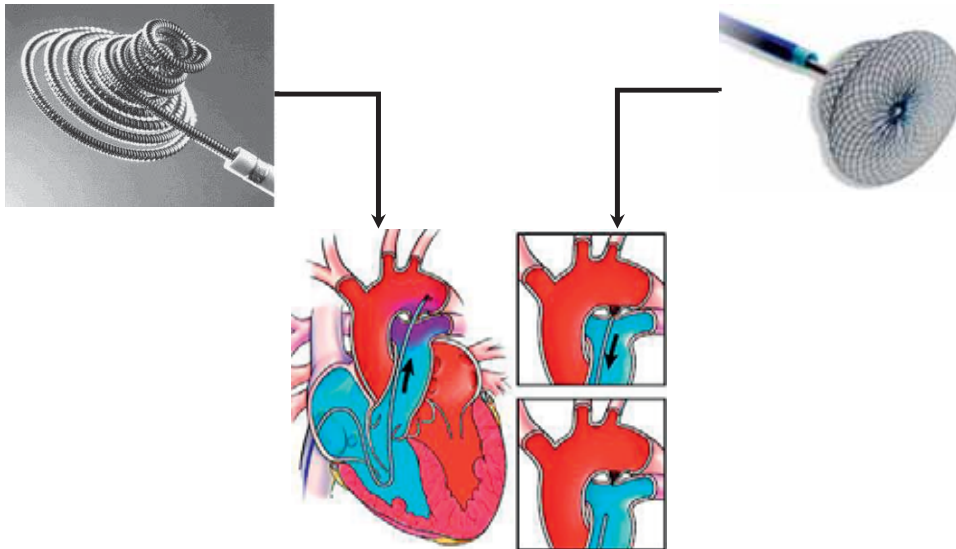
A. Medical

- Control heart failure & prevent infective endocarditis (Infective endarteritis)
- Medical closure in preterm by I.V. indomethacin in the 1st week of life .

B. Transcatheter or Surgical closure

Irrespective of age, size or symptoms ,all PDAs should be closed, preferably before 1 yr of age.

- **Small PDAs** are closed with intravascular coils
- **Moderate to large PDAs** are closed with an umbrella-like device



Differential diagnosis of continuous murmurs:

- An aorticopulmonary window defect
- A sinus of Valsalva aneurysm that has ruptured into the right side of the heart or pulmonary artery, Coronary arteriovenous fistulas
- Truncus arteriosus
- VSD with aortic insufficiency, and combined aortic and mitral insufficiency (to-and-fro murmur rather than continuous nature)

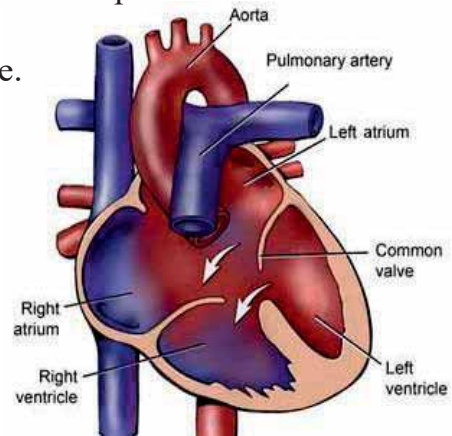
Atrio ventricular septal defect (AVSD) (Endocardial cushion defect; ECD)

Definition

Defect in atrioventricular septum; complete defect is composed of:

- 1- Large ASD
- 2- Common & incompetent atrio ventricular valve.
- 3- Large VSD.

Association: common with Down syndrome.



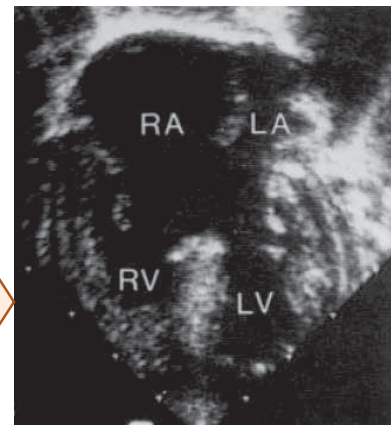
Manifestations

- Features of increased pulmonary blood flow and intractable heart failure develop early in infancy.
- Evidence of cardiomegaly and hyperactive precordium (RVH mainly)
- Systolic thrill on lower left sternal border.

Auscultation

- 1- Lower left sternal border → Pansystolic murmur propagating all over the precordium
- 2- Pulmonary area → Systolic murmur of a relative pulmonary stenosis or pulmonary hypertension

Clinical picture is very similar to large VSD and cases are only diagnosable by Echocardiography



Treatment

1. Medical: - As for large VSD
2. Surgical
 - Because of the risk of pulmonary vascular disease developing as early as 6-12 mo of age, Early surgical repair is mandatory to avoid early pulmonary hypertension and intractable heart failure
 - Complication :surgically induced heart block requiring placement of a permanent pacemaker
 - Pulmonary artery banding is an option as a palliative surgery

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Coarctation of Aorta (CoA)

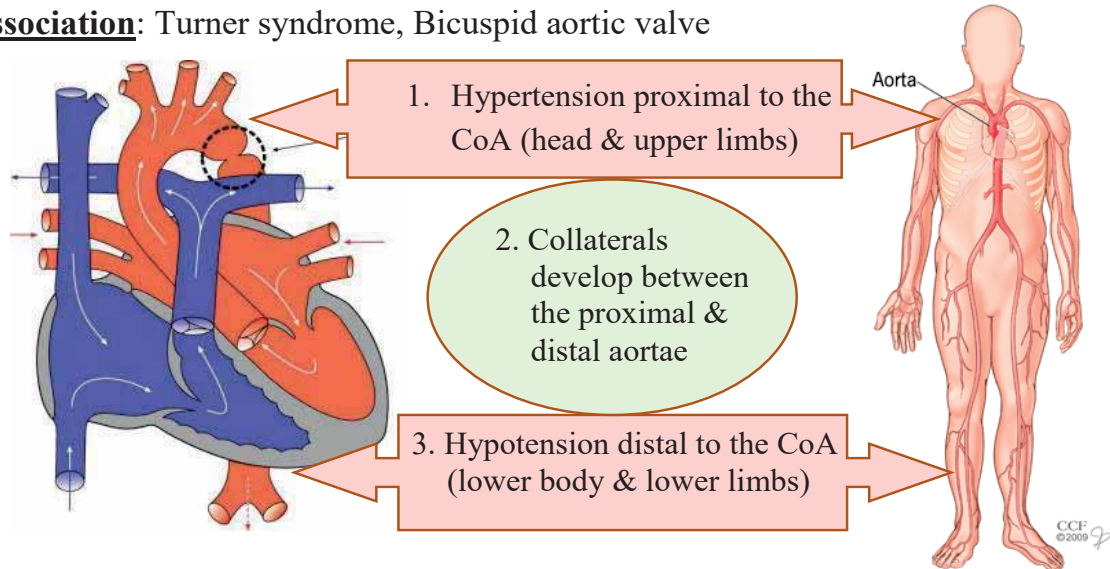
Constriction of the aorta to anywhere from aortic arch to aortic bifurcation.

Types

Ductal CoA: adjacent to ductus arteriosus; below origin of left subclavian artery

Preductal or postductal CoA : far uncommon

Association: Turner syndrome, Bicuspid aortic valve



4. In severe coarctation , blood is shunted from the pulmonary artery to the descending aorta via a patent arterial ductus with subsequent:
- Perfusion of the lower body is dependent on the patent ductus(duct dependent systemic flow)
 - May be differential cyanosis (lower limbs blue, upper limbs pink).

Clinical Picture

1. Severe coarctation

- Usually no symptoms are apparent at birth, but can develop within a week of birth with the closure of the ductus arteriosus
- Presentation: poor feeding, congestive heart failure, cardiomegaly and acidosis

2. Milder cases: Usually asymptomatic; may present in older child or adult with:

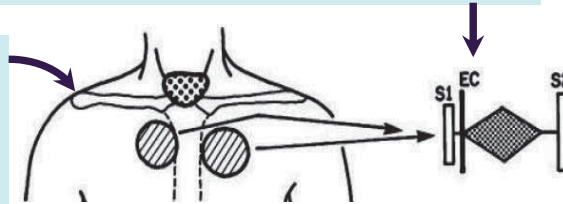
- **Pulse**
 - Bounding in upper limbs and carotids , weak or absent in lower limbs
 - Femoral pulse is delayed than radial pulse (unlike normal).
- **Blood pressure** :Higher in upper limbs than lower limb(unlike normal)
The upper-to-lower extremity pressure gradient will increase with exercise

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- **Murmur**

- Systolic murmur with ejection click
- Over the base of the heart
- Transmitted to the left infrascapular area

In older patients with well-developed collaterals:
A continuous murmur may be heard over chest laterally and posteriorly



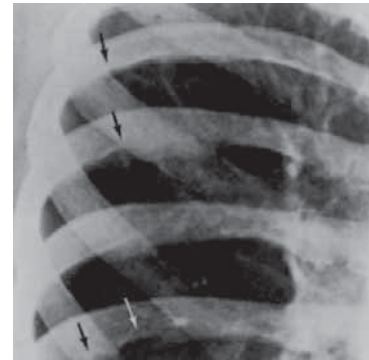
3. Complicated cases: May present with:

- * Systemic hypertension due to renal hypoperfusion.
- * Intracranial hemorrhage due to hypertension or associated aneurysm of circle of Willis.

Investigations

1- Chest X-ray:

- Cardiomegaly (LVH)
- Notching of the inferior border of the ribs from pressure erosion by enlarged collaterals is common by late childhood (Rosler sign)



2- ECG: - LVH in older patients

3- Echocardiography is Diagnostic

4- When echocardiogram is equivocal: cardiac CT , MRI and catheter are alternative diagnostics

Treatment

1. In neonates with severe coarctation of the aorta

- Infusion of prostaglandin E1 to reopen the ductus and re-establish adequate lower extremity blood flow.
- Once a diagnosis has been confirmed and the patient is stabilized, surgical repair should be performed

2. Older cases require:

- Control of hypertension and prophylaxis against infective endocarditis.
- Surgical repair

Cyanotic Congenital Heart Disease (CCHD)

Classification

CCHD with decreased pulmonary blood flow	CCHD with increased pulmonary blood flow
<u>With RVH</u> <ul style="list-style-type: none"> - Fallot tetralogy - Pulmonary atresia with VSD <u>With LVH</u> <ul style="list-style-type: none"> - Tricusped atresia - Ebstein anomaly - Pulmonary atresia with VSD 	<u>With RVH</u> <ul style="list-style-type: none"> - Transposition of great arteries (TGA) - Total anomalous pulmonary venous return - Eisenmenger Syndrome <u>With BVH</u> <ul style="list-style-type: none"> - Truncus arteriosus - Single ventricle
<u>Criteria</u> <ul style="list-style-type: none"> - Hypercyanotic spells (attacks of increasing cyanosis) - Heart failure is very rare - P₂ (pulmonary component of S₂) → ↓ - Chest X-ray → lung oligoemia 	<ul style="list-style-type: none"> - Poor feeding "dyspnea on suckling". - Recurrent chest infections is common - Recurrent heart failure is common - P₂ → ↑ - Chest X-ray → plethora.
- Growth retardation occurs in long standing, symptomatic, uncorrected lesions.	

Central cyanosis

Definition

Bluish discoloration of skin and mucous membranes due to presence of > 5 gm /ml reduced hemoglobin in the capillary blood.

Causes

1. Congenital heart diseases are the main cause of chronic central cyanosis
 - The commonest cyanotic congenital heart disease is Fallot tetralogy.
 - The commonest cyanotic congenital heart disease presenting at birth is TGA.
2. Respiratory failure (usually acute cyanosis)

Presentation

- Early it may be overlooked and become evident only during crying and feeding
- Then it becomes apparent at rest; noted mainly in inner lips and tongue

Consequences

- Cyanotic clubbing, dusky blue skin, gray sclerae with engorged blood vessels
- Polycythemia
- Increased risk of Relative iron deficiency and Cerebral stroke

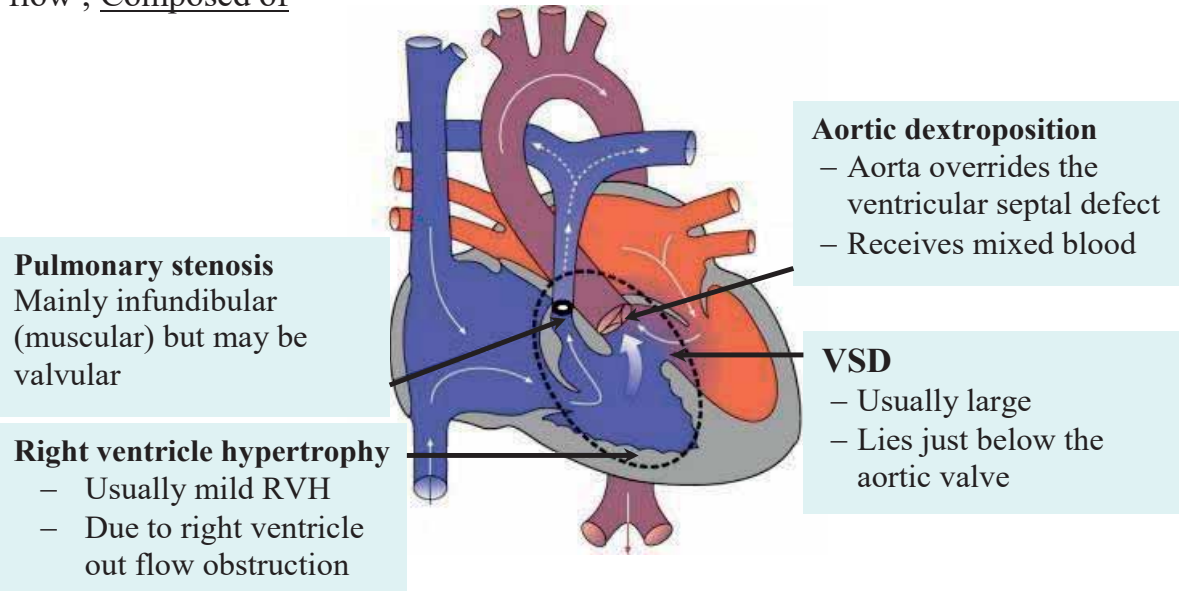
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CCHD with decreased pulmonary blood flow

Fallot Tetralogy

Definition

Commonest cyanotic congenital heart disease with decreased pulmonary blood flow ; Composed of



Hemodynamics

A. Degree of pulmonary stenosis (PS) determines degree of right to left shunt:

1. Severe PS

- Early right to left shunt → cyanosis appear in the neonatal period
- Pulmonary blood flow is mainly dependent on flow through the ductus arteriosus
- When the ductus begins to close in the 1st few hours or days of life, severe cyanosis and circulatory collapse may occur

2. Mild to moderate PS

Patient is initially pink; over time, pulmonary stenosis gradually increases → right to left shunting → cyanosis appear within months

B. Pulmonary blood flow is maintained

- In neonate via ductus arteriosus
- In older child via Multiple aortopulmonary collateral arteries arising from the ascending and descending aorta

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Clinical picture

1. Central Cyanosis



- Often, cyanosis is not present at birth; but with increasing hypertrophy of the right ventricular infundibulum as the patient grows, cyanosis occurs later in the 1st year of life
- Infants with severe degrees of PS, neonatal cyanosis is noted immediately
- Infants with mild degrees of PS may initially be seen with heart failure caused by a ventricular-level left-to-right shunt
- Cases who aren't initially visibly cyanotic are termed Acyanotic or pink Fallot .

2. Cyanotic Clubbing of fingers and toes

3. Growth retardation (Stunting) in unrepaired cases

4. Squatting position



- Older children ,with significant cyanosis at rest, have dyspnea on exertion
- After physical effort → dyspnea increases → the child assumes squatting position for the relief of dyspnea
- Theory: Squatting →kink of femoral arteries →↑ systemic vascular resistance →↑ aortic pressure →↑ pulmonary blood flow →↑ blood oxygenation.

5. Paroxysmal hypercyanotic Spells (Hypoxic, "blue," or "tet" spells)

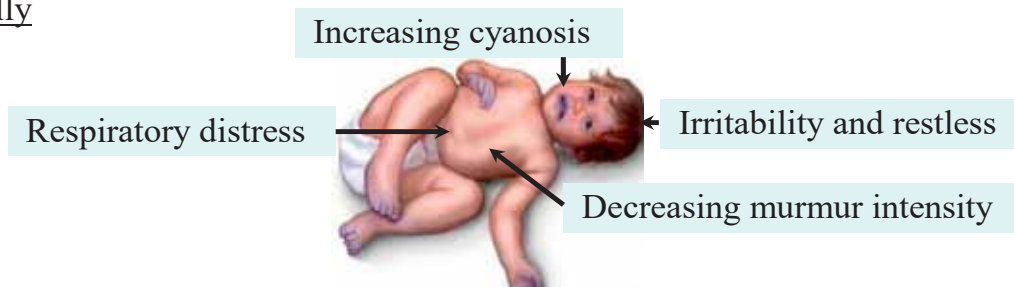
Incidence

Mainly in the 1st 2 years of life; triggered by crying, feeding or infection

Mechanism

Infundibular spasm → reduction of an already reduced pulmonary blood flow→ if prolonged→ severe systemic hypoxia and metabolic acidosis

Clinically



- Spell lasts from a few minutes to a few hours
- Severe spell may lead to convulsions, cerebrovascular stroke or even death

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6. Cardiac examination

Precordial

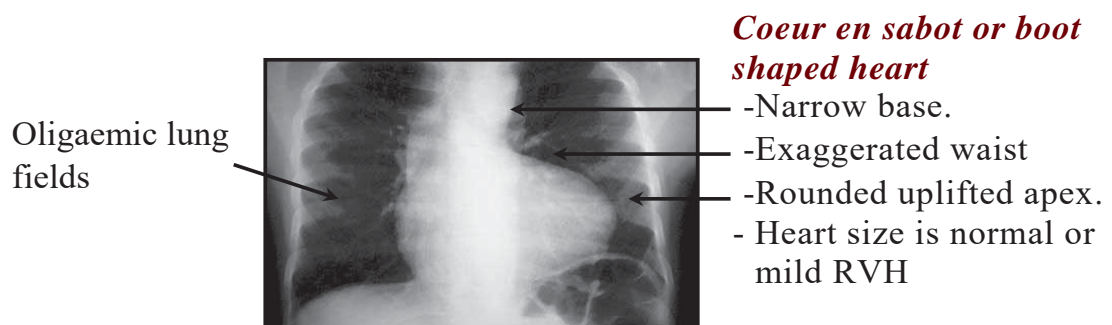
- Normal heart size (may be mild RVH)
- Systolic thrill over left sternal border.

Auscultation

- S₂: single (A₂ only is heard)
- Murmur: systolic (organic PS) on the upper and mid left sternal border.

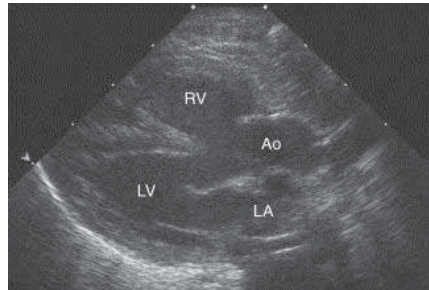
Investigations

1. Chest X-ray



2. Echocardiography

Two-dimensional
Echo is Diagnostic



3. Others

- ECG shows RVH
- Catheter → Pre-operative
- CBC show polycythemia

Complications

Early corrective surgery in infancy made it rare

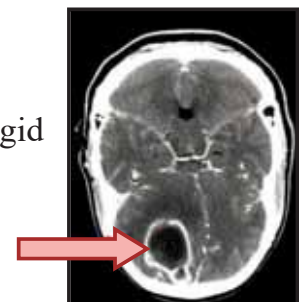
1. Polycythaemia due to

- Hypoxemia → ↑ erythropoietin → polycythaemia
- Relative iron deficiency increase polycythaemia

2. Cerebral thrombosis due to:

- Extreme polycythemia → sluggish blood flow
- Microcytosis due to relative iron deficiency → rigid non deformable RBCs

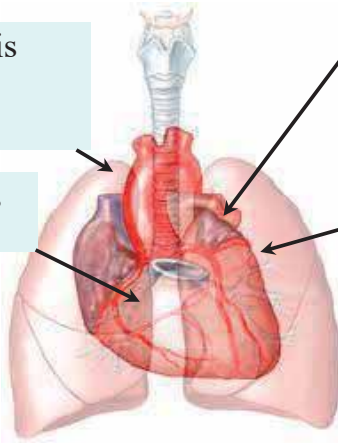
3. Brain abscess due to septic emboli and lack of pulmonary filtration



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4. Pulmonary tuberculosis due to pulmonary oligemia

5. Infective endocarditis



6. Heart failure is rare; may be iatrogenic with big shunt

7. Associated anomalies e.g. *DiGeorge syndrome* or *CATCH 22* (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia).

Treatment

1. Medical

A. Treatment of hypoxic spells (in sequence)

- Don't Panic
- Calm and hold the infant in Knee-chest (frog) position ± pressure to femoral pulses.
- Facial oxygen (if not distressing the child)
- Avoid premature attempts to obtain blood samples to avoid further agitation



- Morphine 0.1mg/kg SC/IM/IV
 - Suppress the respiratory center
 - Caution in infants less than 3 months of age
- Fluid bolus 10ml/kg of NaCl 0.9% or Colloid IV
- Sodium bicarbonate 1mEq/kg IV (= 1ml/kg of 8.4%)
- Improve right ventricle out flow and reduce right to left shunt by either:
 - i. Propranolol 0.1mg/kg IV over 5 minutes.
 - Value : Reduces infundibular spasm
 - Contraindicated if already on maximal dose of oral beta blockers.

OR

- ii. Phenylephrine 5-10mcg/kg (slow IV push)
 - Value: Increases systemic vascular resistance



- PICU Intervention : Intubation and ventilation for spells resistant to the above management



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- After the spell is over:
 - Oral propranolol prophylaxis 0.5-1 mg/kg/6hours
 - Avoid digitalis as it may induce infundibular spasm
 - Arrange for surgery

B. Avoid cerebral thrombosis by

- Treatment of relative iron deficiency
- For severe polycythemia
 - Adequate hydration
 - Phlebotomy
 - Partial exchange transfusion with albumin or saline.

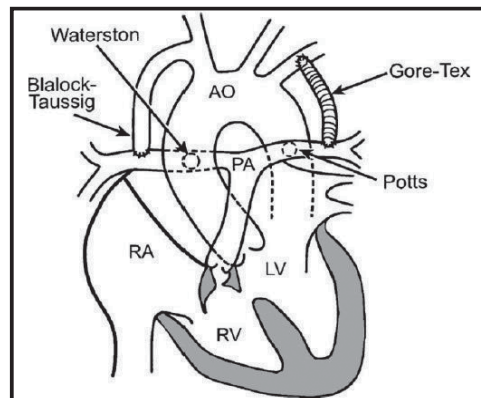
C. Prophylaxis & treatment of infective endocarditis.

2. Surgical

Indicated as soon as the spells begin

A. Palliative shunts

- * Idea: Anastomosis between aorta and pulmonary artery to allow ↑ pulmonary blood flow
- * Modified Blalock Taussig operation:
Anastomosis between subclavian artery & ipsilateral pulmonary artery using Gore Tex conduit (Potts and Waterston operations are obsolete)



B. Total repair:

Can be done between 4 months to 2 years according to severity and available cardiac center

Other causes of CCHD with decreased pulmonary blood flow

- All are Fallot tet. like in clinical presentation and management
- Differentiated from Fallot tet by Echocardiography and diagnostic catheter

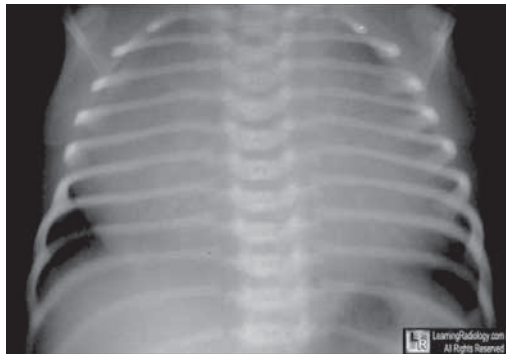
Ebstein's Anomaly

Composed of

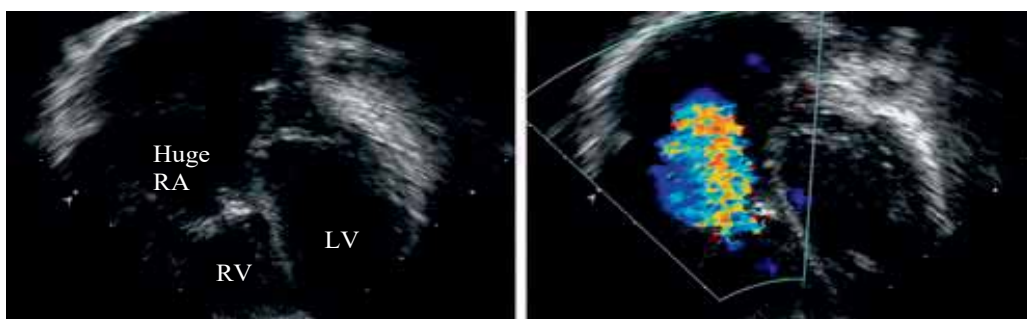
- Huge right atrium
- Downward displacement of tricusped valve leaflets.
- Tricusped regurge is common.
- Small right ventricle

Clinically

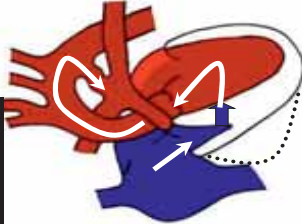
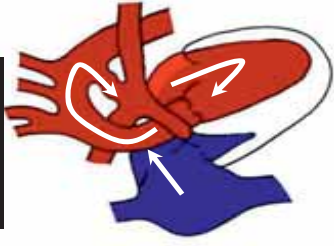
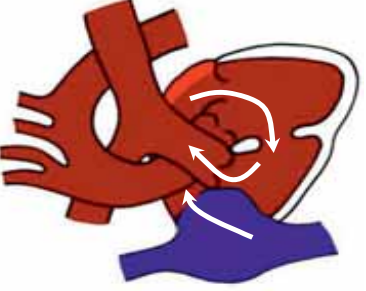
- May be asymptomatic
- Splitting of S1 and S2
- May be
 - Mild cyanosis
 - Atrial arrhythmias
 - Pansystolic murmur (tricusped regurge)
- May be heart failure.
- Chest X-ray: May be huge cardiomegaly in.



- ECG → Right bundle branch block (RBBB) and RAD
- Echocardiography and color Doppler : diagnostic



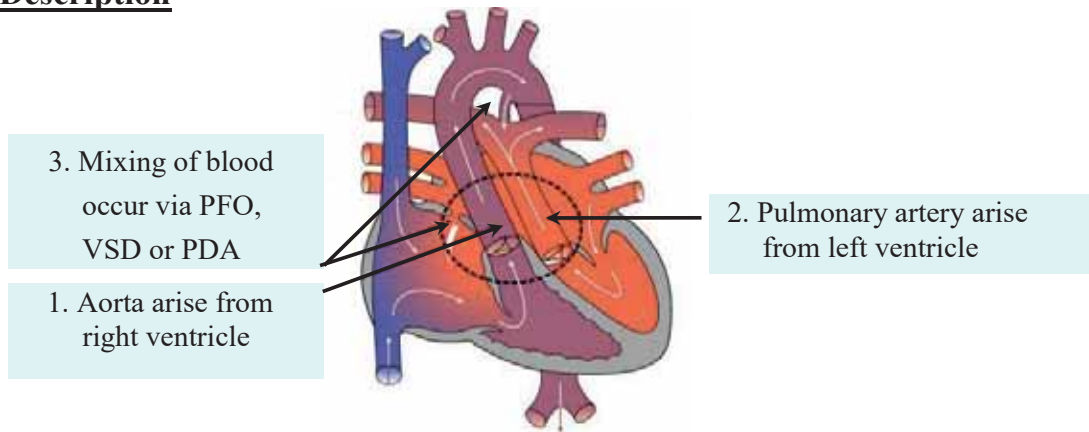
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3. Pulmonary atresia		4. Tricuspid atresia
<p><u>With VSD</u></p>  <ul style="list-style-type: none"> • Blood in right. ventricle pass to left ventricle via VSD so, Left ventricle contain mixed Blood → cyanosis. • Pulmonary blood flow depends on PDA or collaterals between Aorta & pulmonary artery. 	<p><u>Without VSD</u></p>  <ul style="list-style-type: none"> • Blood in right atrium pass via patent foramen ovale (PFO) → left atrium → left ventricle → cyanosis. • PFO & PDA are essential for life. 	 <ul style="list-style-type: none"> • Atrietic tricuspid valve → Blood in right atrium pass via PFO → left atrium → left ventricle → cyanosis. • Pulmonary blood flow is dependent on VSD or PDA. • Right ventricle is hypoplastic.
<p><u>Presentation</u></p> <ul style="list-style-type: none"> - Cyanosis is evident at birth → increase in intensity with ductus arteriosus closure. - Single second heart sound (only A₂ is heard). - No murmurs. (may be machinery of PDA or collaterals). 		
<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> - Echocardiography can differentiate it from Fallot tetralogy. 		
<p><u>Treatment</u></p> <ul style="list-style-type: none"> - Once suspected after birth: PGE₁ infusion to keep the ductus open - Operative: Palliative shunts/ Total correction - Medical: measures for polycythemia and infective endocarditis(as before) 		

CCHD with increased pulmonary blood flow

1. Transposition of Great arteries (TGA)

Description



Incidence: Common in infant of diabetic mother.

Types: - Isolated TGA

- TGA With VSD
- TGA With VSD and pulmonary stenosis
- Corrected TGA

Isolated (intact ventricular septum)	TGA With VSD
<p>Medical emergency</p> <ul style="list-style-type: none"> * Severe cyanosis at birth * With ductus closure → marked cyanosis with acidosis and hypoglycemia * No murmur * Single accentuated S₂ (anteriorly placed aorta) 	<ul style="list-style-type: none"> - Milder cyanosis - Manifestations of increased pulmonary blood flow - VSD murmur.

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Investigations

☞ Chest x ray

- Cardiomegaly (egg on side)
- Plethoric lung



☞ ECG: RVH.

☞ Echo.: Diagnostic

☞ Cardiac catheter: Preoperative

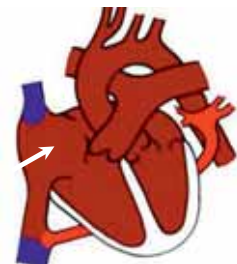
Treatment

- | | |
|--|---|
| 1- Maintain PDA → PGE ₁ infusion & avoid O ₂ .
2- Palliative operation: <u>Rashkind</u> balloon atrial septostomy → create large ASD → free intra cardiac mixing.
3- Total correction: either
- Arterial switch operation (anatomical correction)
- Atrial switch operation. | - Treatment of heart failure (3D).

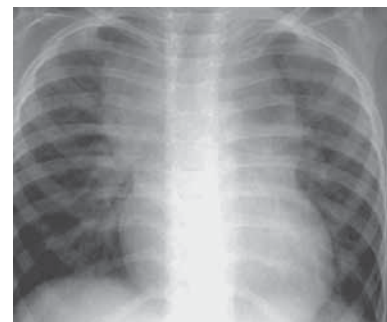
- Arterial switch operation |
| 4- Other lines of treatment: - Avoid cerebral thrombosis (see Fallot tet)
- Precautions against infective endocarditis | |

2. Total anomalous pulmonary venous return (TAPVR)

- Pulmonary veins drain into right side of the heart either:
 - In superior vena cava (supra cardiac)
 - In coronary sinus (cardiac)
 - In inferior vena cava (infra cardiac)
- ASD allow blood in right atrium to pass to left atrium → blood mixing → cyanosis.



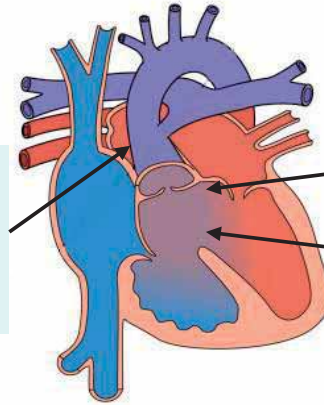
- Chest X-ray
Snowman in snowstorm **or**
Figure 8 shaped heart.
- Echo is diagnostic



3. Truncus arteriosus (TA)

Description

1. One arterial trunk leave the heart giving rise to both aorta & pulmonary artery



2. One semilunar valve (Truncal valve)

3. Large VSD below the trunk

Types

Type I	Type II	Type III	Type IV "pseudo truncus"
Single pulmonary artery from left. Side	Two pulmonary arteries from the posterior wall	Two pulmonary arteries from the lateral wall	Arteries arising from the descending aorta → supply the lungs.

Clinical picture

- Cyanosis → variable onset (usually minimal esp. in neonate & infants).
- Features of increased pulmonary blood flow
- S_2 → single.
- VSD murmur.
- Chest X-ray → Right sided aortic arch in 50% of cases.

Treatment

1. Treatment of heart failure.
2. Surgical correction.

4. Single ventricle

- *Absent interventricular septum* → both Aorta & pulmonary artery arise from common ventricle → free mixing of blood → cyanosis.
- Degree of cyanosis depends on whether pulmonary valve is stenotic or not which determine pulmonary blood flow.

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Valvular lesions

1. Mitral Stenosis (MS)

Causes

- 1- Rheumatic (mainly)
- 2- Congenital (rarely)

Hemodynamics

- MS → Blood accumulate in left atrium → left atrial dilatation
→ pulmonary congestion and pulmonary congestive symptoms
- Prolonged pulmonary congestion → pulmonary hypertension with low cardiac output symptoms
- Prolonged pulmonary hypertension → Right ventricular hypertrophy & right ventricle failure → systemic congestive symptoms

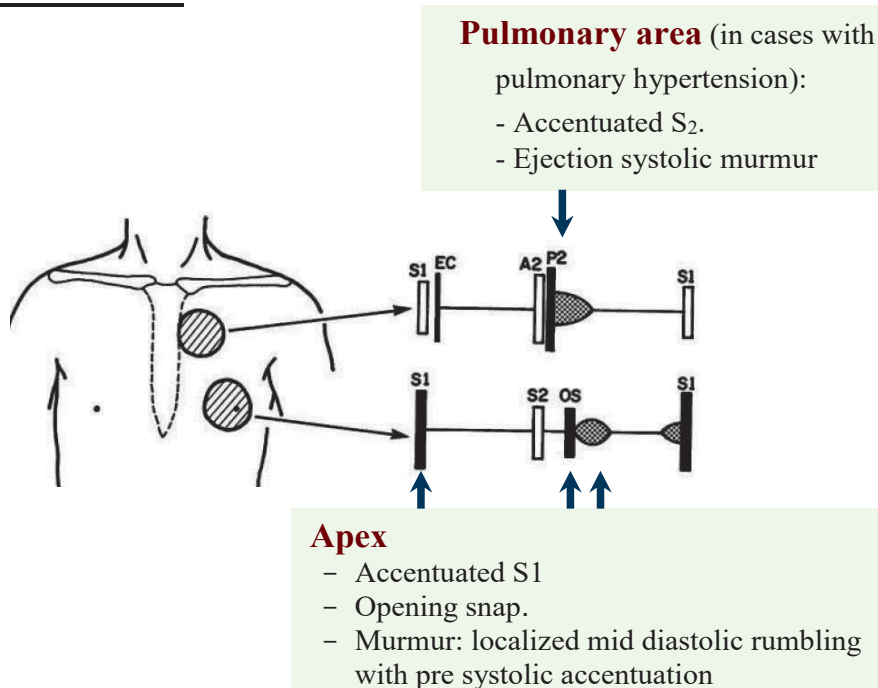
Symptoms

- Mild cases may be asymptomatic ; discovered accidentally
- Pulmonary venous congestive manifestations with or without systemic venous congestive manifestations.

Precordial examination

1. Weak apex beat; Slapping apex due to palpable first heart sound.
2. Pulmonary pulsation (palpable second heart sound) and dull pulmonary area in cases with pulmonary hypertension.

Auscultation



Complications

- * Valve
 - Rheumatic activity
 - Bacterial endocarditis
 - Calcification
- * Left atrium
 - Dilatation → compression manifestations
 - Dysrhythmias
 - Intra atrial thrombi
- * Ventricle
 - Right ventricular failure

2. Aortic Regurge (AR)**Causes**

- 1- Rheumatic (mainly)
- 2- Syphilitic, Marfan syndrome or post-operative (rare).

Hemodynamics

- 1- Incompetent aortic valve → In diastole blood returns to the heart leading to:
 - Decreased diastolic pressure.
 - Large end diastolic volume of left ventricle → increased systolic pressure.
- 2- High systolic pressure and low diastolic pressure result in hyperdynamic circulation.

Symptoms

- 1- Manifestations of low cardiac output.
- 2- Palpitation with exertion.

General examination: (peripheral signs suggesting A.R.)

1. Corrigan sign = visible arterial pulsations in carotid arteries.
2. De Musset sign = head nodding with each heartbeat.
3. Wide pulse pressure.
4. Water hammer pulse.
5. Capillary pulsations (in nail beds and lips).
6. Hill's sign: Lower limb's systolic pressure is higher than upper limb by > 20 mmHg.
7. Pistol shot due to push of blood in an empty artery.
8. Duroisier sign: diastolic murmur on pressing femoral artery by distal edge of stethoscope.

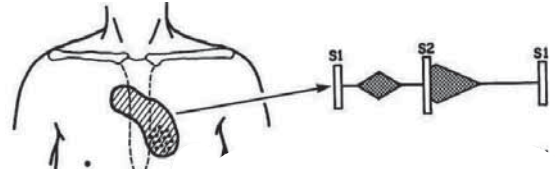
Precordial examination

- Hyper dynamic apex (forcible, non-sustained).
- Left ventricular enlargement (LVH).

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Auscultation**Aortic area**

1. Early diastolic murmur
 - On the 1st & 2nd aortic areas
 - Increases by leaning forward & in expiration
 - Propagates to the apex
2. May be ejection systolic murmur due to functional aortic stenosis

**3. Mitral regurge (MR)****Causes**

- 1- Rheumatic (mainly)
- 2- Congenital (rarely)
- 3- Mitral valve prolapse

Hemodynamics

- 1- Incompetent mitral valve → in systole blood returns to the left atrium → left atrial dilatation and pulmonary congestion → pulmonary hypertension.
- 2- Large end diastolic volume of left ventricle → left ventricle enlargement.

Symptoms

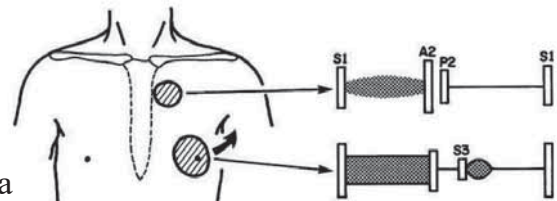
- May be asymptomatic in early cases
- Palpitation with exertion.
- Pulmonary venous congestive manifestations.

Precordial examination

- Hyper dynamic apex. (forcible, non-sustained).
- Left ventricular enlargement (LVH).
- May be apical systolic thrill.
- May be evidence of pulmonary hypertension (dull, pulsating pulmonary area)

Auscultation**1. Apex**

- Muffled S₁.
- Murmur → Pansystolic.
→ Propagates to the axilla

**2. Pulmonary area**

In cases with pulmonary hypertension:

- Accentuated S₂.
- Ejection systolic murmur.

Aortic stenosis (AS)

Causes

1. Rheumatic	2. Congenital
Valvular stenosis - The commonest - About 70%	a. Valvular: bicusped aortic valve b. Subvalvular: a membrane or septal hypertrophy (hypertrophic obstructive cardiomyopathy) c. Supravalvular (With <i>Williams syndrome</i> : Elfin facies, hypercalcemia, Cocktail party chatter).

Hemodynamics

- Left ventricle outflow obstruction
 → Low cardiac output.
 → Left ventricle hypertrophy & left ventricle failure.

Symptoms

1. Critical stenosis can present early in life with heart failure
2. Milder cases
 - May be asymptomatic
 - Manifestations of low cardiac output in older child.
 - Manifestations of complications

Precordial examination

- Heaving apex (forcible, sustained).
- Left ventricular enlargement (LVH).
- Systolic thrill over aortic area and the neck.

Auscultation

- Aortic area:
- Muffled, delayed aortic component of S₂.
 - Murmur → Harsh ejection systolic murmur
 → Best heard on 1st aortic area
 → Propagate to the neck & the apex.

Complications

1. Left ventricular failure
2. Bacterial endocarditis
3. Sudden cardiac death

Treatment

- **Medical**
 - Exercise restriction for severe stenosis
 - Prophylaxis against endocarditis
 - Avoid vasodilators
- **Interventional / surgical** (*Balloon valvoplasty or valvotomy or valve replacement*)
For: Symptomatic cases and/ or Pressure gradient across the valve > 40mmHg

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Pulmonary stenosis (PS)

Causes

- Congenital mainly.

Symptoms

- 1- Asymptomatic in mild cases
- 2- Severe obstructive lesions can present early in life with heart failure.
- 3- Manifestations of low cardiac output in older child.

Precordial examination

- Right ventricular enlargement (RVH).
- Systolic thrill over pulmonary area.

Auscultation

Pulmonary area

Muffled pulmonary component of S₂.

Murmur → Ejection systolic on pulmonary area propagate to the left parasternal area.

Investigations of valvular lesions

Investigations	Value
Chest x ray	<ul style="list-style-type: none"> - Detect cardiomegaly - Pulmonary vascular markings: <ul style="list-style-type: none"> - Oligemic in pulmonary stenosis - Prominent in left sided failure - Specific configuration
ECG	<ul style="list-style-type: none"> - Detect chamber enlargement - Myocardial ischemia
Echocardiography	- Diagnostic ; see before
Catheterization	<ul style="list-style-type: none"> - Diagnostic ; done pre-operative - Interventional

Treatment of valvular lesions

A. Medical

1. Afterload reducers e.g. captopril for regurgitant lesions.
2. Exercise restriction for severe stenotic lesions.
3. Treat complications:
 - Heart failure
 - Infective endocarditis.
 - Arrhythmias

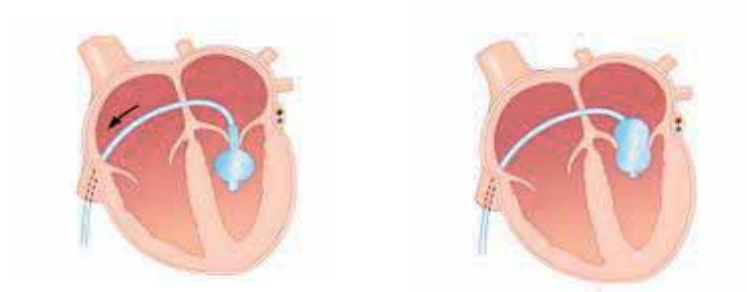
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- 4- Prophylaxis against
- Infective endocarditis.
 - Rheumatic fever (in rheumatic cases).

B. Interventional

Balloon valvoplasty for symptomatic, non-calcific, stenotic lesions e.g.

- AS
- PS
- MS



C. Surgical

- 1- Valvotomy for stenosis
- 2- Valve repair for regurge
- 3- Valve replacement.

Acute Rheumatic Fever (ARF)

Definition

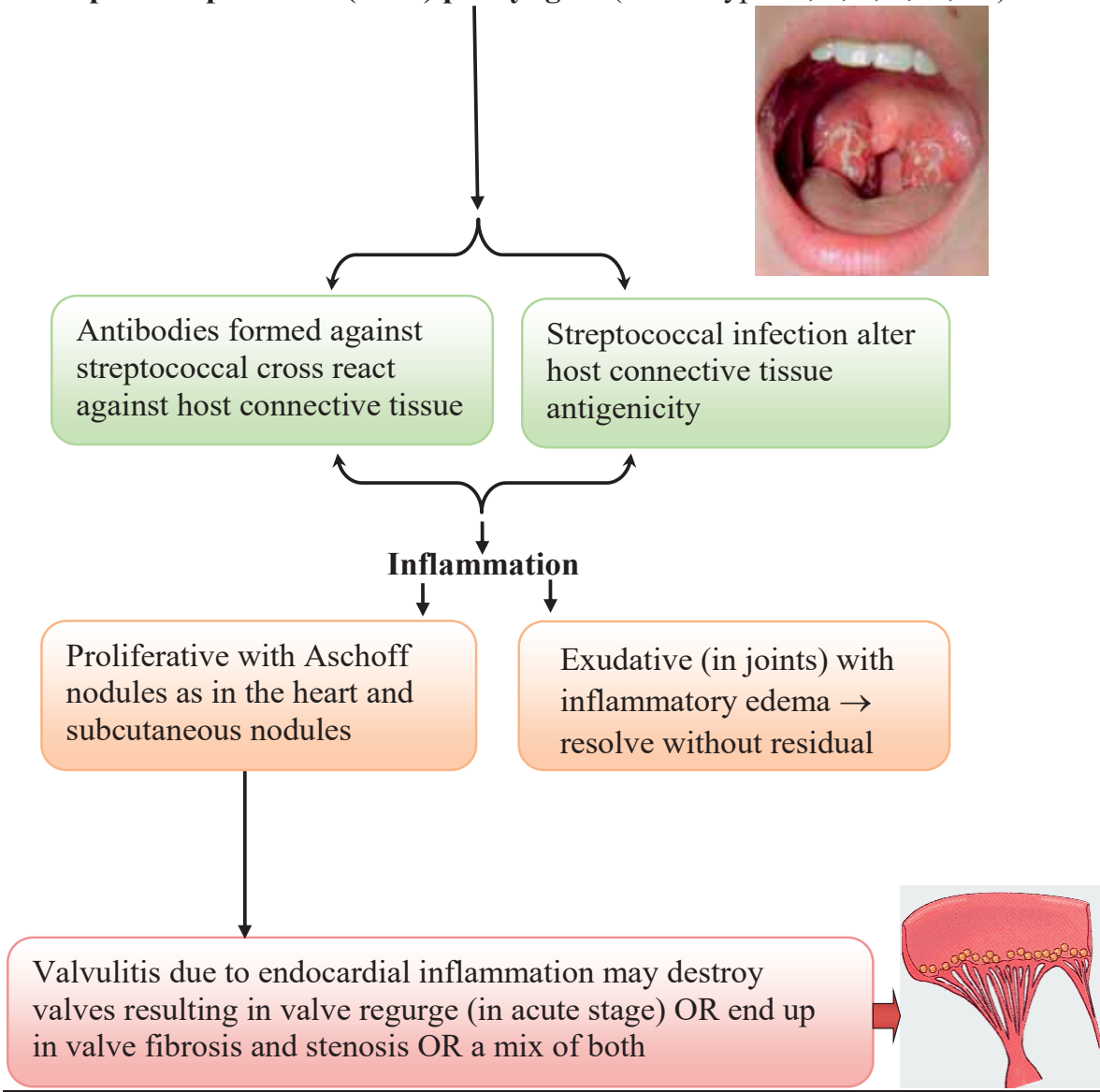
Immunologic disease affecting mainly the heart and joints & less frequently central nervous system, skin and subcutaneous tissue

Risk factors

- Peak of onset between 5-15 year (rare before 5 years)
- Genetic predisposition
- Moderate and High risk populations : Developing countries
- Low risk populations : USA, Canada, western Europe

Pathogenesis

Group A Streptococcal (GAS) pharyngitis (M serotypes 1, 3, 5, 6, 18, 24)



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Clinical Picture

A latent period of 1-3 weeks usually exist between pharyngitis and clinical symptoms of acute rheumatic fever

Major Criteria of Rheumatic Fever

1. Arthritis

- The commonest presenting sign 75%
- Distribution
 - Usually affect big joints (e.g. knee, ankles, wrist, elbow).
 - Polyarticular arthritis; either simultaneous or successive.
 - Migratory arthritis → Fleet from one joint to another.
- Joint examination
 - Inspection → Red, hot, swollen (inflamed)
 - Passive movement → Severely tender
 - Active movement → Absolute limitation of movement
- Course :
 - Dramatic response to salicylates within 48 hours.
 - Resolve without residuals, even without treatment, over one week.
- Arthritis now refers to polyarthritis in low-risk populations, but to monoarthritis or polyarthralgia in moderate/high-risk populations

2. Carditis

- The 2nd common (50%) and most serious manifestation of ARF
- Pancarditis → inflammation of endocardium, myocardium and pericardium
- Carditis may be silent or late onset appearing after 6 weeks – 6 months
- Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis)

i. Endocarditis: Valvulitis

Affect commonly the mitral valve with or without aortic valve:

a. Mitral valve

- Valve edema → transient mitral stenosis → mid diastolic rumbling murmur (*Carey Combs* murmur)
- Valve destruction → mitral regurge → apical holosystolic murmur propagating to the axilla with muffled 1st heart sound.

b. Aortic valve

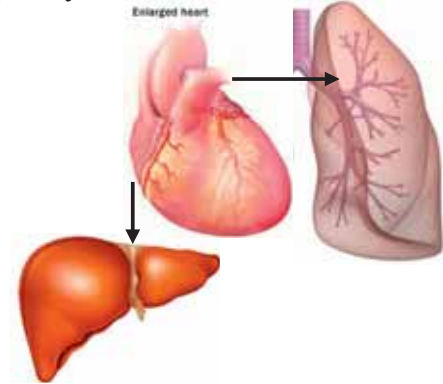
- Aortic regurge → left sternal border early diastolic murmur.



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2. Myocarditis

- Tachycardia out of proportion to age & fever (rarely bradycardia due to heart block)
- Heart failure indicates severe carditis with
 - Marked dyspnea
 - Enlarged tender liver
 - Gallop rhythm, muffled heart sounds
 - Cardiomegaly



3. Pericarditis

a. Dry pericarditis

- Stitching chest pain .
- Pericardial rub (on the bare area of the heart, unrelated to respiration).

b. Pericardial effusion

- Dull aching pain.
- Distant heart sounds.

Investigations for carditis

- ECG may show Low voltage ECG in pericardial effusion.
- Chest x ray may show cardiomegaly
- Echocardiographic findings include mitral and/or aortic regurgitation, pericardial effusion, and decreased ventricular contractility

3. Rheumatic chorea "Sydenham Chorea" (10%)

Incidence

- More in girls 8-12 years (school age).
- Occur weeks or months after pharyngitis so, other criteria are usually lacking.
- May coexist with other rheumatic fever manifestations in 10%

Due to: Dysfunction of the basal ganglia.

Manifestations

1. Emotional lability and personality changes
2. Involuntary movements
 - Sudden ,jerky ,spontaneous pseudo purposeful movements of limbs
 - Facial grimace.
 - Distribution: Proximal more than distal.
 - Increase with emotional stress and decrease by sleep.
3. Hypotonia

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Tests for rheumatic chorea

- Cannot maintain arms extended → spooning & pronation of hands (*Choreic hand*).
- Milk maid's grip: irregular contraction & relaxations on squeezing examiner hand
- Wormian movements of tongue upon protrusion (*Darting tongue*).
- Examination of handwriting to evaluate fine motor movements

Outcome

- Self-limited ; usually resolve within 4-8 weeks
- Acute phase reactant are usually normal in isolated chorea

4. Erythema Marginatum (< 5%)Site

- The trunk
- Proximal parts of the limbs

Criteria

- Large erythematous macules.
- With pale centers and serpiginous borders(map like appearance)
- Evanescent.(may come and go for several months)
- Not pruritic

**5. Subcutaneous Nodules (< 1%)**

Appear several weeks after the attack

Site

- Over the extensor surfaces of tendons near bony prominences.

Criteria

- Size is about 1 cm.
- Firm, freely mobile, and painless.
- Usually associated with severe carditis.



N.B: Both sub cutaneous nodules and erythema marginatum are rare in Egypt

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Minor criteria of Rheumatic Fever

A. Clinical

1. Fever: of $> 38^{\circ} \text{C}$ ($>38.5^{\circ} \text{C}$ in Low-Risk populations)

2. Arthralgia

- Moderate/High-Risk populations only include monoarthralgia (polyarthralgia for Low-Risk populations)
- Can't be used as minor manifestation in presence of arthritis

B. Investigations

1. ECG: Prolonged P-R interval

- Can't be used as minor manifestation in presence of carditis

2. Elevated acute phase reactants

- \uparrow ESR; $>30 \text{ mm/hr}$ ($>60 \text{ mm/hr}$ in Low-Risk populations).
- \uparrow C reactive protein

Evidence of recent Group A Streptococcal (GAS) infection

- Positive throat culture Or
- Elevated or increasing streptococcal antibody titers : ASO , Anti Deoxyribonuclease (DNase) β , Anti hyaluronidase

American heart association's revised Jones criteria (2015)

- **For diagnosis of initial attack of ARF**
 - 2 major manifestations, **Or**
 - 1 major and 2 minor manifestations

Plus

 - Evidence of recent GAS infection
- **For diagnosis of recurrent attacks of ARF**
 - 2 major, **Or**
 - 1 major and 2 minor, **Or**
 - 3 minor manifestations (only in the Moderate/High-Risk population)

Plus

 - Evidence of recent GAS infection
- **Carditis Redefinition** (see before)
- **Arthritis Redefinition** (see before)
- **Minor criteria Redefinition** (see before)

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Notes on Jones criteria

There are 3 circumstances in which the diagnosis of acute rheumatic fever can be made without strict adherence to the Jones criteria:

- When chorea occurs as the only major manifestation of acute rheumatic fever
- When indolent carditis is the only manifestation
- Patients with recurrences of acute rheumatic fever in particularly high-risk populations.

Prognosis and complications

1. Arthritis sub side within days to weeks even without treatment.
2. Chorea subsides within few months without residuals.
3. Only carditis can cause permanent damage especially in recurrences which :
 - * Suggested by:
 - Appearance of new murmurs.
 - Change in character of already existing murmur
 - * Result in organic valve lesion e.g. MS,MR, AS, and/or combined valve lesion.
 - * Carditis and chronic valve lesions may be complicated by:
 - Heart failure
 - Infective endocarditis
 - Embolic manifestations
 - Arrhythmias
 - Pulmonary hypertension

Differential diagnosis

1. Other causes of arthritis

○ Post streptococcal arthritis

- May follow infection with either group A or group G streptococcus
- Typically oligoarticular, affecting lower extremity joints, and mild symptoms can persists for months
- Some clinicians consider it to be an incomplete form of acute rheumatic fever

○ Transient synovitis (toxic synovitis)

- Post-infectious arthritis, typically affects the hip, often after an upper respiratory tract infection
- Acute onset of severe pain in the hip, with referred pain to the thigh or knee, lasting approximately 1 wk

○ Rheumatoid arthritis:

- Chronic deforming arthritis; last ≥ 6 weeks.
- Non migratory
- Some involve small peripheral joints.
- Absent dramatic response to salicylates within 48 hours.
- Associations e.g. Spiking fevers, lymphadenopathy, and splenomegaly

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- Reactive arthritis related to gastrointestinal infections (e.g., **Shigella**, **Salmonella**, **Yersinia**)
- **Septic arthritis** (usually monoarthritis)
- **Serum sickness**
- Hematologic e.g. **Sickle cell disease**, **Acute leukemia** , **hemophilia**.
- Immunologic e.g. **Systemic lupus erythematosus**& **anaphylactoid purpura**

2. Other causes of carditis e.g.

- Vial carditis
- Infective endocarditis
- Drug induced.

3. Other causes of chorea e.g

- Wilson disease
- Cerebral palsy

Treatment of Acute Rheumatic Fever

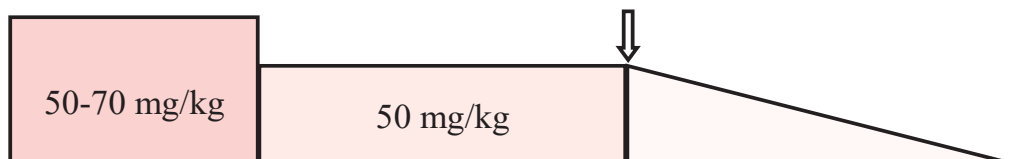
A. Treatment of Acute Attack

1. Eradicate group A Streptococci from the upper respiratory tract

- Oral penicillin or erythromycin for 10 days or a single intramuscular injection of benzathine penicillin
- Long-term antibiotic prophylaxis after this initial course of antibiotic therapy

2. Typical migratory Arthritis

1. Bed rest for 2 weeks
2. Anti-inflammatory drug: Salicylates



- Dose: 50-70 mg/kg/day (max = 6 gram /day) For 3-5 days
 - Then 50 mg/kg/d for 3 weeks.
 - Then gradual withdrawal monitored by decline in ESR & CRP
 - Side effects: Gastritis, GI bleeding(R/Gastriprotection),Reye syndrome
3. Daily examination is vital to pick carditis that can present within 2 weeks of the onset

3. Carditis

1. Bed rest

- For cases with severe carditis and heart failure
- Rest for 3 months and gradual ambulation for a similar period



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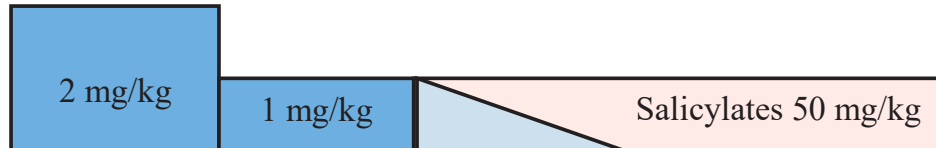
2. Anti-inflammatory drugs

a. Corticosteroids (Prednisone)

* Indications:

- Moderate to severe carditis(with cardiomegaly)
- Heart failure.

* Dose:



- 2 mg/kg/d for 2-3 weeks
 - Followed by half the dose for 2-3 wk
 - And then tapering of the dose by 5 mg/24 hr every 2-3 days.
- At the beginning of tapering; salicylates is started at dose of 50 mg/kg/d and continued for 6 weeks to avoid rebound phenomenon.

b. Salicylates can be used in mild carditis without cardiomegaly nor heart failure

3. Heart failure with respiratory distress

a. Oxygen inhalation

b. Restriction of salt and fluid intake.

c. Steroids

d. Other anti-failure drugs:

- Diuretic: Furosemide 1mg/kg every 6-12 hours
- VasoDilators: e.g. captopril
- Digoxin: used cautiously; begin with half the usual recommended dose

(Nelson Textbook of Pediatrics, 2016)

- Anti-inflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute rheumatic fever.
- Premature treatment with one of these agents may interfere with the development of the characteristic migratory polyarthritis and thus obscure the diagnosis of acute rheumatic fever.
- Acetaminophen can be used to control pain and fever while the patient is being observed for more definite signs of acute rheumatic fever or for evidence of another disease

(Nelson Textbook of Pediatrics)

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4. Treatment of Rheumatic Chorea

- Avoid emotional stress.
- Control abnormal movements:
 - Phenobarbitone 16-32 mg / 8 hours oral Or
 - Haloperidole (Safinase tablet) 0.01-0.03 mg/kg.
- Long acting penicillin prophylaxis.

5. Treatment of complications

- Treatment of heart failure; see before.
- Treatment of infective endocarditis
- Treatment of valve lesions

B. Prophylactic

1. Primary prevention: prevent 1st attack by:

- Hygienic housing.
- Proper treatment of Strept. infection: penicillin **or** erythromycin for 10 days.

2. Secondary prevention : Prevent recurrence of Rheumatic fever by:

- Long acting penicillin (Benzathine penicillin)
- Dose : 600.000 units for those < 27 kg and 1.2 million unit for those > 27 kg
- Route: Single injection, I.M every **3-4** weeks.
- Alternatives: Oral penicillin V **or** Macrolide (Erythromycin)
- Duration

Rheumatic fever category	Duration
- Without carditis	- 5 yr or until 21 yr of age, whichever is longer
- With carditis but without residuals	- 10 yr or until 21 yr of age, whichever is longer
- With carditis and residual heart disease	- 10 yr or until 40 yr of age, whichever is longer - Sometimes lifelong prophylaxis

(Nelson Textbook of Pediatrics, 2016)

3. Infective Endocarditis (IE) prophylaxis

- American heart association (AHA) no longer recommends routine IE prophylaxis for rheumatic heart diseases
- Prophylaxis is still recommended only for those with prosthetic valves or prosthetic material used in valve repair (use antibiotic other than penicillin)

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Infective endocarditis

Definition

- Infection of the valvular & mural endocardium
- Infection can be bacterial, viral, or fungal

Pathogenesis

Two factors are essential

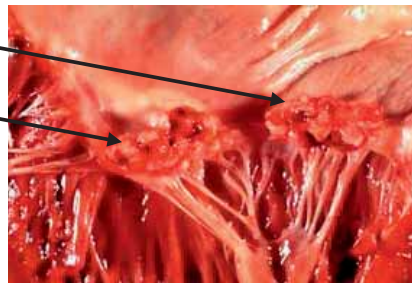
1. Presence of cardiac structural abnormality with significant pressure gradient
2. Bacteremia; even transient

Commonest causative organisms

1. Streptococcus viridans (50%):
 - Follows dental surgery ,dental caries, tonsillectomy, dental extraction
2. Staphylococcus aureus and epidermidis
 - Mainly postoperative
 - Risk is high with prosthetic valve and central venous catheter
3. Group D enterococci
 - More often after lower bowel or genitourinary procedures
4. HACEK group : Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella species
4. Pseudomonas aeruginosa or Serratia marcescens
 - Seen more frequent in intravenous drug users
5. Fungal: Seen more frequent in immunodeficient & post open heart surgery.

Pathology

Implantation of the organism in the diseased endocardium → Local inflammation & formation of friable *vegetations* composed of platelets, fibrin, inflammatory cells, and organisms



Clinical picture

A. History: Suggestive of a risk factor or bacteremia

B. General manifestations

1. Fever (pyrexia)
2. Poor appetite → weight loss & malaise.
3. Palpable spleen (tender splenomegaly)
4. Pale clubbing
5. Pallor
6. Purpura



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7. Rare manifestations due to immune complexes induced vasculitis:

Osler nodules

- Transient tender nodules
- Pea-sized
- Intradermal in the pads of the fingers and toes



Janeway macules

- Irregular, painless macules
- In palms and soles



Splinter hemorrhage

- Linear hemorrhagic streaks
- Beneath the nails



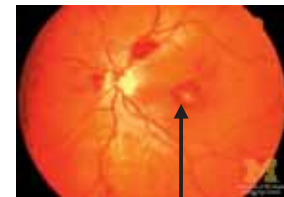
B. Cardiac manifestations

- Appearance of new murmurs
- Change in the character of previous murmurs
- Sea gull murmur (musical) → due to rupture of valve leaflets.
- Heart failure or arrhythmias.

C. Embolic manifestations

1. Neurologic

- Embolic stroke (seizures, hemiparesis)
- Cerebral abscess
- Mycotic aneurysm → intracranial hemorrhage

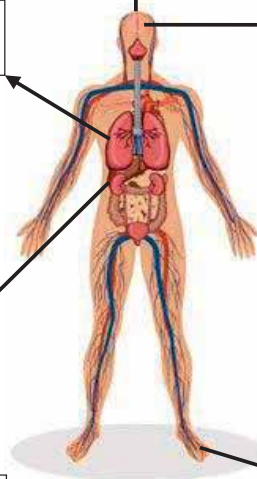


2. Pulmonary embolism

3. Retinal hemorrhages;
(Roth spots = oval with pale centers), blindness



4. Renal infarction →
hematuria & renal failure



5. Skin infarcts and
gangrene

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Investigations

A. For diagnosis

1. Blood culture
 - 3-5 blood samples before the start of antibiotics (contact the lab staff !!!)
 - The causative agent is recovered from the 1st 2 blood cultures in 90% of cases
2. Echocardiography: transthoracic and transesophageal

Value

 - Detects vegetations (early & minute vegetation < 3 mm³ may be missed)
 - May predict embolization (fungating vegetation > 1 cm³).
 - Detects underlying cardiac lesions
 - Detects complication e.g. valve dysfunction or leak , myocardial abscess
3. Culture of other specimens may include scrapings from skin lesions, urine, synovial fluid, abscesses, and, CSF in case of meningitis
4. With unusual microorganisms
 - PCR of surgical material e.g. resected valve tissues
 - Specific serology

B. For monitoring/effect

1. Acute phase reactant (ESR, CRP, Procalcitonin and Leucocytosis)
2. Complete blood count: for anemia of chronic illness
3. Renal function tests, urinalysis

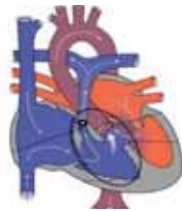
Prevention

A. Oral and dental care;the important

B. Antibiotic prophylaxis; Required for cases with:



1. Prosthetic cardiac valve
or prosthetic material used
for cardiac valve repair



3. Congenital heart disease
(except ASD)



4. Repaired Congenital heart disease
with prosthetic material or device

5. Palliative shunts and conduits



2. Previous infective endocarditis



6. Permanently damaged valves
due to Rheumatic heart disease



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Procedures requiring prophylaxis ?

- Dental /oral
- Invasive respiratory tract procedures
- Cardiac surgery/catheterization



- Prophylaxis for gastrointestinal or genitourinary procedures is no longer recommended in the majority of cases
- Direct consultation with the child's cardiologist is still the best method for determining a specific patient's ongoing need for prophylaxis

Prophylactic antibiotics

- Oral amoxicillin (50 mg/kg) or Ampicillin Or
- Ceftriaxone (50 mg/kg) IM or IV Or
- If penicillin allergic: Azithromycin or clindamycin

3. Vigorous treatment of sepsis and local infections

Treatment

Medical

- 1- Hospitalization, Bed rest and treat heart failure
- 2- Antibiotic therapy
 - Start immediate parenteral antibiotic combinations while waiting for culture results.
 - For 4-6 weeks (modify in view of clinical and laboratory response)
 - Best empirical therapy in patients without a prosthetic valve is vancomycin plus gentamicin
 - Other antibiotics include crystalline penicillin G, ceftriaxone, nafcillin or oxacillin.
 - Amphotricin B and 5 fluorocytosine for fungal endocarditis.

Surgical

- Removal of vegetation with or without valve replacement
- Indications
 - Treatment failure e.g. increasing size of vegetations while under therapy
 - Complications: Severe valve involvement with intractable heart failure, myocardial abscess, recurrent emboli

(American Heart Association 2007, Nelson 2016)

Prognosis: Despite the use of antibiotic agents, mortality is at 20-25%. Serious morbidity occurs in 50-60%

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Heart failure

Definition

Clinical syndrome in which the heart is unable to pump enough blood to meet body needs.

Causes

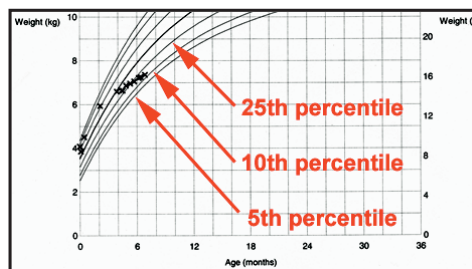
Congenital heart diseases are the commonest causes of heart failure in infancy	Rheumatic heart diseases (in school age)
<ul style="list-style-type: none"> ▪ Myocarditis <ul style="list-style-type: none"> - Viral e.g. Coxsackie A, B & Echo viruses - Toxic e.g. drugs, diphtheria . ▪ Dilated cardiomyopathy. ▪ Infective endocarditis 	<ul style="list-style-type: none"> ▪ Acute hypertension ▪ Severe anemia
<u>Dysrhythmia</u> <ul style="list-style-type: none"> ▪ Supraventricular tachycardia ▪ Complete heart block 	<ul style="list-style-type: none"> ▪ Acute cor pulmonale ▪ Broncho pulmonary dysplasia
<ul style="list-style-type: none"> ▪ Nutritional e.g. Beri Beri, Kwashiorker, Keshan disease(selenium deficiency) 	

Clinical features

A. Symptoms

Infants

- Poor feeding; takes less volume per feeding, becomes dyspneic while sucking, and may perspire profusely
- Poor weight gain.



Older child

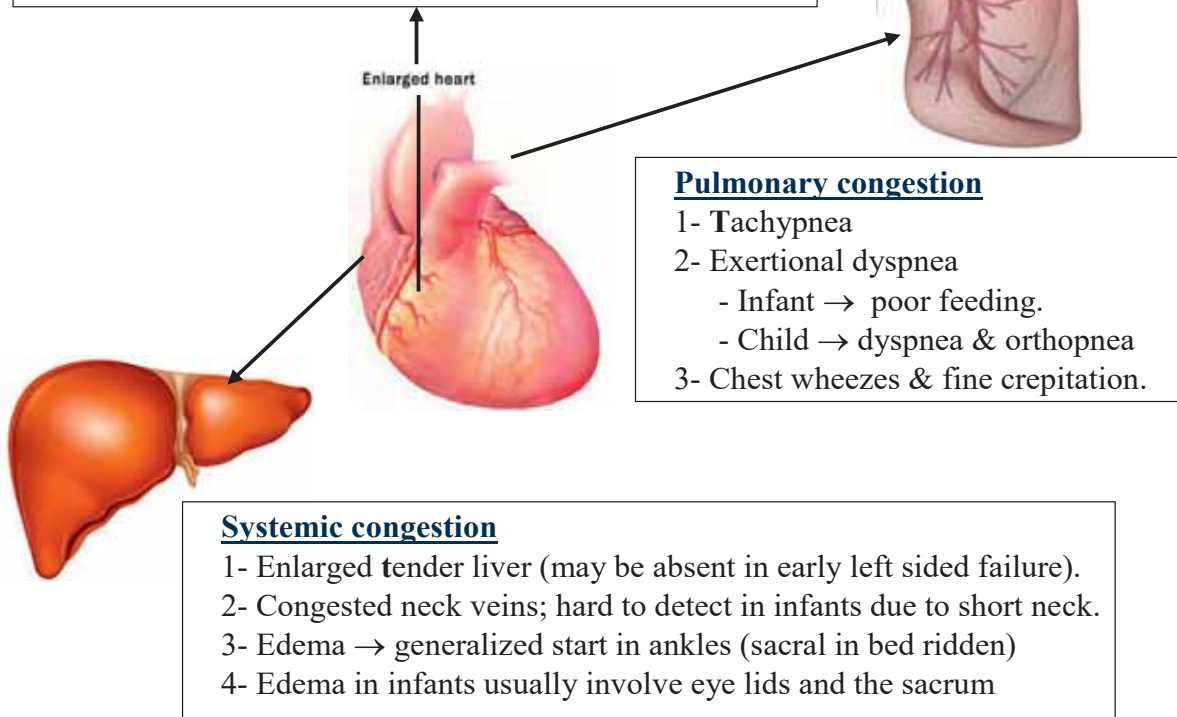
- Dyspnea on exertion.
- Effort intolerance.
- Ankle edema.

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B. Signs

Compensatory response to heart failure

- 1- Tachycardia, gallop rhythm & weak pulse.
- 2- Cardiomegaly is almost always present.
- 3- Cold, sweaty skin (increased sympathetic drive)



Investigations (Heart failure is a clinical diagnosis)

1. Chest X-ray



- Cardiomegaly
- Fluffy perihilar pulmonary markings

2. Echocardiography



- Confirm ventricular dysfunction
 - Using fractional shortening (difference between end-systolic and end-diastolic diameter divided by end-diastolic diameter)
 - Normal value is between 28% and 42%
- Doppler can estimate cardiac output
- May detect the cause of failure.

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3. Magnetic resonance angiography (MRA)

- Quantifies left and right ventricular function, volume and mass.
- Quantifies the regurgitant fraction in valvar regurgitation

4. ECG: - Detect arrhythmias.

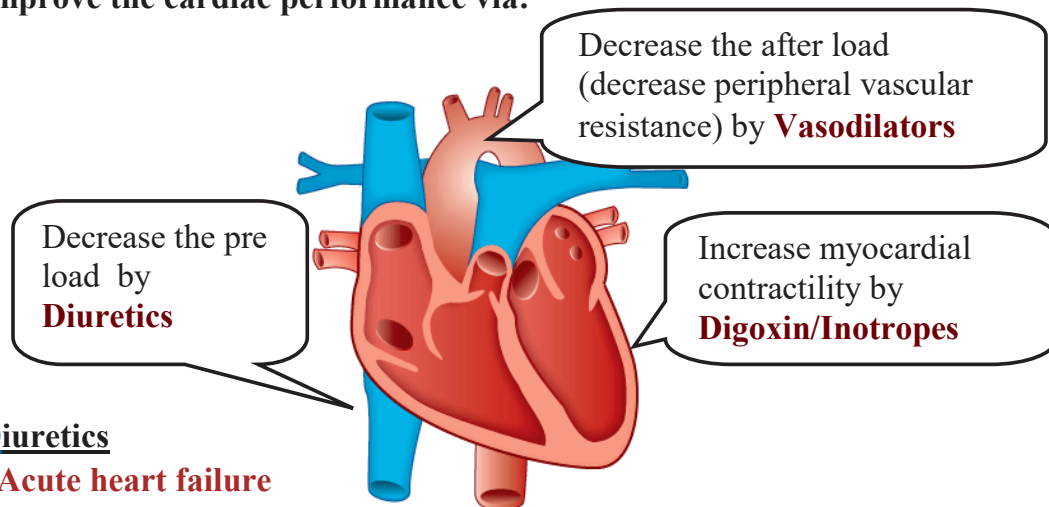
Treatment

1. Hospitalization

- o Bed rest as needed in a semi-upright position (infant chair for infants)
- o O₂ inhalation ± positive pressure ventilation can significantly reduce total body oxygen consumption
- o Low salt diet → avoid further salt and water retention.
- o Increasing daily calories (nasogastric feedings may be helpful)
- o Sedation

2. Treat the cause

3. Improve the cardiac performance via:



a. Diuretics

Acute heart failure

- Furosemide
 - I.V. (0.5-2 mg/kg/dose) or oral (1-4 mg/kg/day)
 - Precautions : monitor serum electrolytes and acid base (Hypokalemia and alkalosis → may increase digitalis toxicity)
- Nesiritide (B-type natriuretic peptide) IV infusion

Chronic heart failure

- Spironolactone (potassium sparing diuretic)
- Thiazide diuretics

b. Vasodilators

Used if blood pressure allows and in absence of obstructive lesions

Actions

- After load reducers
- Cardiac remodeling

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Commonly used drugs

- Angiotensin converting enzyme (ACE) inhibitors e.g. Captopril, Enalapril
- Angiotensin receptor blockers [ARBs]

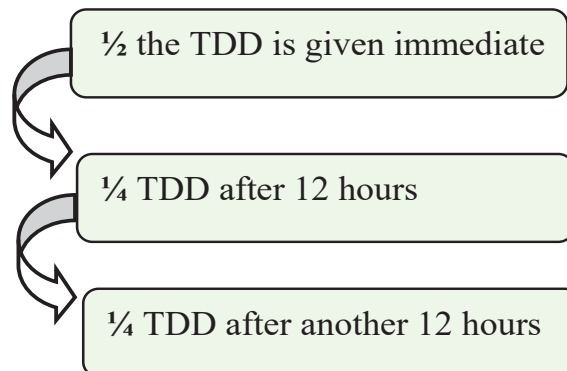
Indicated mainly in:

- Dilated cardiomyopathy/myocarditis
- CHD with large left to right shunt.
- Severe MR and AR
- Hypertensive heart failure

c. Digoxin**Digitalization**

- o Total digitalizing dose (TDD)

	Oral TDD (microg/kg)	I.V. TDD
Premature	20	75% of oral T.DD.
Newborn	30	
Infants < 2 y	40-50	
Child > 2 y	30-40	



- o Precautions
 - Obtain ECG before each of the 3 digitalizing doses
 - Measure baseline serum electrolyte before and after digitalization
- o Maintenance dose
 - Oral: 5-10 µg/kg/day, divided q12h
 - IV dose is 75% of oral dose
 - Trough serum level: 1.5-3.0 ng/mL <6 mo old; 1-2 ng/mL >6 mo old

Absolute contraindications to digitalis

- Cardiac outlet obstruction e.g. Hypertrophic cardiomyopathy.
- Fallot's tetralogy
- Heart block.

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Other inotropes

- Used for short term in ICU setting ;given by intravenous infusion
- Dobutamine ± Dopamine
- Milrinone(Phosphodiesterase inhibitor)

Digitalis toxicity**1. Causes**

- Accidental over dose.
- Renal impairment.
- Increased myocardial sensitivity e.g.: hypokalemia & active myocarditis
- Drug interactions.

2. Signs

- Anorexia, vomiting
- Drowsiness & visual disturbance in older child.
- Bradycardia
- Worsening of heart failure.
- Arrhythmias (supraventricular arrhythmia & heart block).

3. Treatment

- Continuous ECG monitoring.
- Stop digitalis
- Correct hypokalemia
- Correct arrhythmias by
 - a- Atropine 0.01 mg/kg/6 hours for heart block.
 - b- lidocaine for ventricular arrhythmia
- Increase excretion of digoxin by Digoxin immune Fab (*Digibind*), slow I.V.





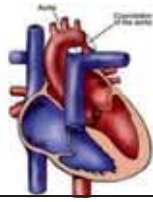

Systemic Hypertension

Definition

- Average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is ≥ 95 th percentile for age, sex, and height on ≥ 3 occasions
- Prehypertension was defined as average SBP or DBP that are ≥ 90 th percentile but < 95 th percentile
- In adolescents beginning at age 12 yr, prehypertension is defined as BP between 120/80 mm Hg and the 95th percentile

Causes

1. Essential (primary) hypertension
 - Rare in children; common in adults.
 - Associations \rightarrow obesity, hereditary, increased sensitivity to salt intake.
2. Secondary

Etiology	Acute	Chronic
Renal 	- Acute glomerulonephritis. - Acute renal failure. - Hemolytic uremic syndrome.	- Renal tumors, hypoplasia, dysplasia. - Chronic pyelonephritis - Hydronephrosis/reflux nephropathy. - Renovascular: <ul style="list-style-type: none"> ○ Renal artery stenosis, thrombosis, ○ Polyarteritis. ○ Renal vein thrombosis.
Endocrine 		- Cushing syndrome - Hyperaldosteronism - Congenital adrenal hyperplasia. - Hyperparathyroidism(hypercalcemia)
Tumors 		- Neuroblastoma - Wilm's tumor. - Pheochromocytoma
Cardiac 		- Coarctation of aorta 
Neurologic 	- Acute \uparrow intra cranial tension. - Guillian Barre syndrome - Poliomyelitis.	
Drugs	- Sympathomimetics.	- Steroids - NSAIDs

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Possible mechanisms in 2ry hypertension

- Stimulation of Renin-Angiotensin-Aldosterone system e.g. renal hypertension.
- Salt & water retention e.g. Cushing & hyperaldosteronism.
- Stimulation of vasomotor center e.g. neurologic hypertension.
- Vasoconstriction due to:
 - ↑ Release of catecholamines e.g. pheochromocytoma
 - Sympathomimetic drugs.

Presentation

- 1- Usually asymptomatic.
- 2- May be → headache, irritability, blurr of vision (in severe cases)
- 3- Complications

- * Hypertensive heart failure.
- * Acute pulmonary oedema.
- * Hypertensive encephalopathy :
 - Severe bursting headache, vomiting,
 - Irritability, convulsions and coma.
 - Fundus examination
 - Vasospasm
 - Papilloedema
 - Retinal hemorrhage.

**Investigations**

- 24 hour Ambulatory Blood Pressure Monitoring (ABPM).
- Calculate mean daytime BP, and sleep BP over 24 hr.
- ABPM is useful in the evaluation for:
 - White coat hypertension
 - Risk of hypertensive target organ damage
 - Response to pharmacologic therapy (confirms physiologic nocturnal dipping of blood pressure essential for kidney vitality)

**Workup for 2^{ry} causes****1. Renal**

- Urine analysis, urine culture, renal function tests.
- Abdominal ultrasound.
- Renal Doppler.
- **If blood pressure is not controlled on ≥ 2 drugs**
 - Pre and post captopril renal scintigraphy and or
 - CT or MRI angiography
- **If strong suspicion of renovascular hypertension**
 - Digital Subtraction Angiography
 - Selective renal vein rennin level

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2. Cardiac

- Chest X-ray
- Echocardiography (For a cause or effect of hypertension).

3. Endocrinal

- Electrolytes (potassium & sodium).
- Night time blood or salivary cortisol level → ↑ in Cushing.

4. Tumors

- 24hr urine vallynile mandilic acid (VMA); (metabolite of catecholamines) → ↑ in pheochromocytoma & Neuroblastoma.
- Abdominal ultrasound, CT, MRI.

Treatment

- Children with BP between the 95th and 99th percentile plus 5 mm Hg are categorized as *stage 1 hypertension*
- children with BP above the 99th percentile plus 5 mm Hg have *stage 2 hypertension*.
- Stage 1 hypertension, if asymptomatic and without target organ damage, allows time for evaluation before starting treatment
- Stage 2 hypertension calls for more prompt evaluation and pharmacologic therapy

Goals

- Reduce BP below the 95th percentile
- In the presence of chronic kidney disease, diabetes, or target organ damage, the goal should be to reduce BP to less than the 90th percentile
- If blood pressure between 90 -95th percentile continue monitoring

A. Chronic hypertension

I. Primary hypertension

1. Non pharmacologic

- Weight reduction may result in a 5-10 mmHg reduction in systolic pressure
- Low salt, potassium rich diet
- Dynamic aerobic exercises
- Physical fitness

2. Drug therapy

Indications

- Family history of early complications of hypertension
- Target organ damage (ocular, cardiac, renal, neurologic)
- Symptomatic hypertension

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Stepped care approach

- ⊕ Step 1: A small dose of single antihypertensive drug either diuretic or an adrenergic inhibitor
- ⊕ Step 2: If the first drug ineffective a second drug is added to or substitute the initial drug starting with small dose then proceed to a full dose.
- ⊕ Step 3: If blood pressure is still high a third drug; usually a vasodilator, is added

Drugs

- * Diuretics e.g. hydrochlorothiazide, chlorothiazide, spironolactone
- * Adrenergic inhibitor e.g. atenolol, prazosin
- * Vasodilator e.g.
 - Hydralazine
 - ACE inhibitors e.g. captopril , enalapril
 - Calcium channel blockers e.g. nifedipine, amlodipine

II. Secondary hypertension

- Treat the cause whenever possible
- Drug therapy as in essential hypertension

B. Acute hypertension

- The blood pressure should be reduced by 10% in the 1st hour, and 15% more in the next 3-12 hr, but not to normal during the acute phase of treatment
- Hypertensive urgencies, usually accompanied by few serious symptoms such as severe headache or vomiting, can be treated either orally or intravenously.

Action plan

1. Ensure safe airway, breathing and circulation (ABC)
2. Slow reduction of blood pressure is mandatory.
3. Drugs useful in acute hypertension:

With severe symptoms

- Hydralazine 4 hourly IM, IV
- Labetalol IV infusion
- Esmolol IV infusion
- Nicardipine IV infusion
- Sodium nitroprusside IV infusion

***With less severe symptoms PO***

- Clonidine, hydralazine, or isradipine.
- Minoxidil is the most potent oral vasodilator; long-acting

4. Treat the cause (in 2nd hypertension).
5. After adequate control of acute hypertension shift to oral antihypertensives

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Hematology

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الدفعة الـ 14

Introduction to Pediatric Hematology

Intrauterine hematopoiesis passes into 3 stages:

Yolk sac hematopoiesis	Visceral hematopoiesis	Medullary hematopoiesis
In the 1 st 8 weeks	8 th week → 6 th month	6 th month → onwards
In the yolk sac	In the liver, spleen, lymph nodes & thymus	Settles in the bone marrow

Exposure to hematologic stress (e.g. chronic hemolysis) → ++ bone marrow then ++ extramedullary hematopoiesis in the spleen and the liver.

Bone marrow contain pluripotent stem cells which give colony forming unit (CFU):

- Erythroid → Erythroblasts → Normoblasts → Reticulocytes → RBCs
- Myeloid → Myeloblast → Promyelocyte → Myelocyte → Metamyelocyte → mature WBCs
- Megakaryocytic → Megakaryoblast → Megakaryocyte → Platelets

• **Normal erythropoiesis requires**

Regulatory hormones

- Erythropoietin
- Androgen
- Thyroxin
- ACTH
- Cortisol
- Growth hormone



• Normal stem cells in bone marrow

Essential nutritional elements

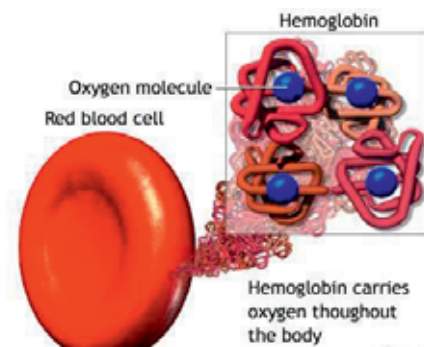
- Proteins
- Iron
- Folic acid
- Vitamin B12
- Copper

Hemoglobin (Hb) composition

Hb molecule is composed of Heme groups (ferrous iron containing) attached to 4 polypeptide chains which define the type of Hb.

Types of normal hemoglobins

1. **Embryonic hemoglobin :**
 - Gower 1, 2 and Portland
 - Disappear by the 3rd month
2. **Foetal hemoglobin**
 - Hb F (α_2, γ_2)
 - Has high affinity to O₂
3. **Adult hemoglobin:** Hb A (α_2, β_2), Hb A₂ (α_2, Δ_2)



Switch mechanism in hemoglobin synthesis

	Embryonic life	6 th month	At Birth	6-12 month postnatal
Embryonic	Dominant	--	--	--
Hb F	--	90 %	70 %	< 1 %
Hb A	--	10 %	30 %	97 %
Hb A ₂	--	--	Trace	2 %

* At the 3rd – 6th month → normal switch from γ to β chain production occurs

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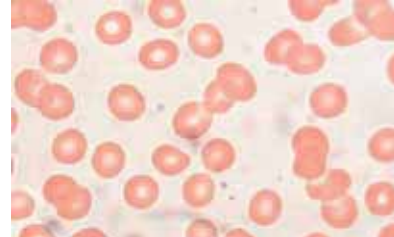
Blood indices

▪ **Hemoglobin content:**

- In 1st 2 weeks → 16-20 gm/dl (intrauterine hypoxia → ↑erythropoietin).
- In infancy → 10-14 gm/dl
- Adult male → 13.5- 17.5 gam/dl
- Adult female → 11.5 – 15.5 gm/dl

▪ **RBCs count:**

- In newborn → 6 million / mm³.
- Adult male → 4.5- 6 million / mm³
- Adult female → 4 - 5.5 million / mm³



▪ **Hematocrite value(Ht. value) ; packed red cell volume**

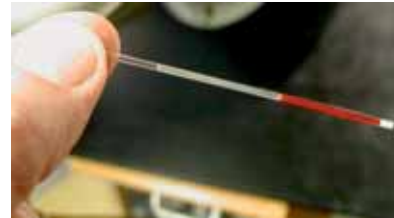
* Percent of RBCs volume in 100 ml blood ≈ 40-50%

* Increased in

- Polycythemia
- Hemoconcentration(dehydration)

* Reduced in

- Anemia
- Hemodilution



▪ **Mean corpuscular volume (MCV)**

- Normal: 72 – 79 femto liter.
- If < 70 → RBCs are small (Microcytes).
- If > 85 → RBCs are big (Macrocytes)

▪ **Mean corpuscular hemoglobin (MCH)**

- Normal: 27- 34 pg.
- If < 27 pg → RBCs are hypochromic.

▪ **Mean corpuscular hemoglobin concentration (MCHC)**

- Concentration of Hb. in an erythrocyte
- Normal: 33%
- If < 30 % → RBCs are hypochromic

▪ **Reticulocytic count (RC)**

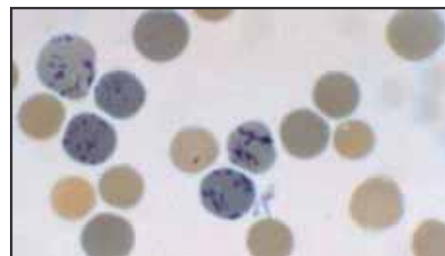
* In neonatal period < 5 %

* Later on 0.5 – 1.5 %

* Reticulocytosis occur in:

- Hemolytic anemia.
- Hemorrhage
- Response to hematinic e.g. (iron, folic acid)
- Recovery of bone marrow from suppression.

* Reticulocytopenia occur in bone marrow failure



▪ **White blood cells count**

- In neonatal period = 15.000 – 20.000 / mm³
- Later on = 4.000 – 11.000 / mm³

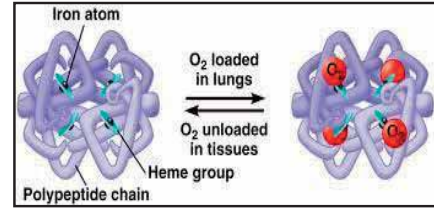
▪ **Platelet count 150.000 – 450.000 / mm³**

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Anemia

Definition

Reduction of hemoglobin and/or RBCs count
Below the average value for age and sex
Interfering with oxygen carrying capacity of blood



General features of anemia

Symptoms (all are non-specific)	Signs (all are non-specific)
<ul style="list-style-type: none"> - Fatigue, headaches and faintness are all very common - Palpitations - Breathlessness - Angina - Intermittent claudication 	<ul style="list-style-type: none"> - Pallor - Tachycardia (palpitation) - Hemic murmurs (functional, systolic). - Heart Failure in severe anemia (with hemoglobin < 4 gm/dl)

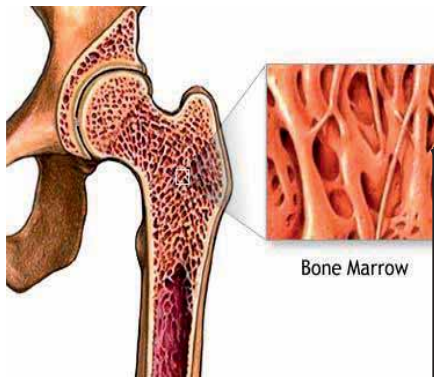
Classification of anemia

A. Morphologic Classification

	Microcytic anemia	Normocytic anemia	Macrocytic anemia
MCV	< 70 fl	72-79 fl	>85 fl

B. Etiologic Classification

I. Decreased production



a. Decreased erythroid cells in bone marrow (Bone marrow failure)

- Pure red cell anemia.
- Aplastic anemia
- Marrow infiltration e.g. Leukemia

b. Decreased red cells production despite normal RBCs precursors

* Anemia of chronic disease:

- Chronic inflammation
- Chronic infection
- Chronic renal failure

c. Specific factor deficiency (Dyshemopiotic anemia) e.g. deficiency of

* Minerals: Iron, copper

* Vitamins: B1, B6, Folic acid and B12.

* Protein

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II. Increased destruction (hemolytic Anemia)

A. Intra corpuscular causes

a. Membrane defects

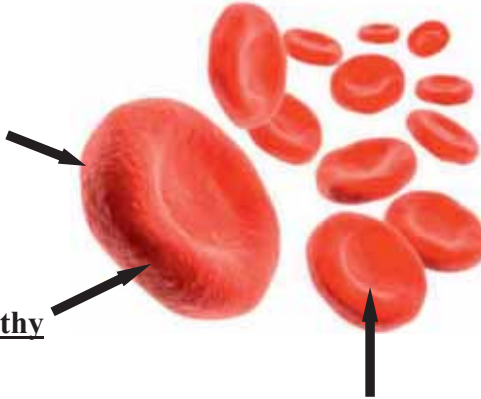
- Hereditary spherocytosis
- Hereditary elliptocytosis.
- Paroxysmal nocturnal hemoglobinuria

b. Hemoglobinopathy

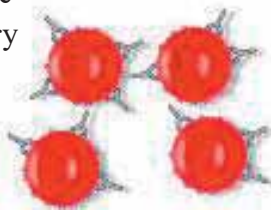
- α thalassemia
- β thalassemia.
- Sickle cell disease

c. Enzymatic defects

- G6PD deficiency
- Pyruvate kinase deficiency.



B. Extra corpuscular causes

Immunologic (Coombs test Positive)	Non immunologic (Coombs test Negative)
1. Iso immune hemolytic anemia (passively acquired antibodies) <ul style="list-style-type: none"> - Hemolytic disease of newborn - Incompatible blood transfusion 	1. Microangiopathic Hemolytic Anemia (MAHA) <ul style="list-style-type: none"> - DIC - Hemolytic Uremic Syndrome (HUS). - Renal Vein Thrombosis (RVT). - Artificial & Calcified Cardiac Valves - Disseminated Cancer - Thrombotic Thrombocytopenic Purpura
2. Autoimmune hemolytic anemia (actively formed antibodies): <ul style="list-style-type: none"> - Idiopathic - Secondary 	2. Septicemia (E.G. Clostridia Welchii) 3. Malaria Due To: <ul style="list-style-type: none"> - Direct Effect - Drug Induced
	4. Drugs, Heavy Metals, Snake Venom 5. March Hemoglobinuria 6. Paroxysmal Nocturnal Hemoglobinuria 7. Hypersplenism

III. Hemorrhagic anemia

- Acute hemorrhage
- Chronic hemorrhage.

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Bone Marrow Failure

A. Trilineage failure

Criteria: - Failure of the 3 cell lines with pancytopenia
- No organomegaly nor lymphadenopathy.

Causes

a. Congenital

1. Fanconi anemia
2. Familial aplastic anemia
3. Dyskeratosis congenital; Ectodermal dysplasia with:
 - Skin pigmentation
 - Mucous membrane leukoplakia
 - Nail dystrophy
 - Others : short stature ,cataract, mental retardation

b. Acquired

1. Idiopathic
2. Secondary

B. One cell line failure

1. Red cells (hypoplastic anemia; pure red cell anemia)

a. Congenital

- Diamond Blackfan anemia
- Congenital dyserythropoietic anemia
- Pearson's Syndrome

b. Acquired

- * Idiopathic: transient erythroblastopenia of childhood
- * Secondary: to Drugs, Infections, Parvo B19 , Malnutrition

2. White cells

1. Schwachman Diamond syndrome: pancreatic insufficiency, metaphyseal dysplasia
2. Kostmann disease (severe congenital neutropenia)
3. Reticular dysgenesis

3. Platelets

1. Congenital amegakaryocytic thrombocytopenia
2. TAR syndrome (thrombocytopenia absent radii syndrome)

N.B : Dyserthropoiesis (ineffective erythropoiesis).

- i. Primary (congenital dyserythropoietic anemia).
- ii. Secondary dyserthropoiesis:
 - Megaloblastic anemia (folic acid, or vit B₁₂ deficiency).
 - Thalassemia syndromes.
 - Sideroblastic anemia.
 - Paroxysmal nocturnal hemoglobinuria

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Aplastic anemia

Definition

Marked decrease **or** absence of blood forming elements in the bone marrow (BM) with peripheral pancytopenia (decreased RBCs, WBCs and platelets).

Etiology

1. Congenital aplastic anemia: e.g. Fanconi anemia
2. Acquired aplastic anemia.
 - ⊞ Idiopathic (50%)
 - ⊞ Secondary
 - Irradiation
 - Insecticides
 - Infections e.g. Epstein Barr virus, hepatitis viruses , HIV
 - Drugs → Dose dependent bone marrow depression e.g. chlorambucil
 - Idiosyncratic non dose dependent BM depression by:

- Antibiotics	→	Chloramphenicol , sulphonamides
- Anticonvulsants	→	Carbamazepine, phenytoin
- Antithyroid	→	Carbimazole, thiouracil
- Antimalarial	→	Chloroquin
- Antirheumatic	→	Indomethacin, phenylbutazone
 - Diseases → SLE, Paroxysmal nocturnal hemoglobinuria (PNH)

Pathogenesis Of acquired aplastic anemia:

- ⊞ Theory: Altered bone marrow stem cells antigen proteins e.g. by drugs or infection → Activated T lymphocytes → ↑ TNF and Interferon γ → accelerated stem cells apoptosis → pancytopenia.
- ⊞ Aplastic anemia is unstable condition; may progress to myelodysplastic syndrome and leukemia

Clinical picture



- Thrombocytopenia → **purpura**
- Anemia → **pallor** (+ weakness, fatigue etc.....)
- Leucopenia → frequent, **persistent** infections
- No organomegaly (*no hepatosplenomegaly nor lymphadenopathy*).

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Fanconi anemia

Inheritance: Mainly autosomal recessive

Clinical features

Skeletal anomalies (60%)

- Abnormal thumb (absent or hypoplastic)
- Absent radii

Short stature with short trunk

Skin pigmentation (café au lait spots) mainly over the trunk



Microcephaly / mental retardation (17 %)
Triangular facies

Congenital anomalies e.g.

- Eye
- Ears
- Cardiac
- Renal
- Genital



Hematological

- High risk of malignancy e.g. acute myeloid leukemia and solid cancers
- Pancytopenia :
 - Typically starts with thrombocytopenia or leukopenia
 - Usually between 4th – 12th year (earlier or later presentation do occur)
 - Bone marrow is aplastic

Investigations

1. CBC

- Pancytopenia (with macrocytic anemia)
- Reticulocytopenia

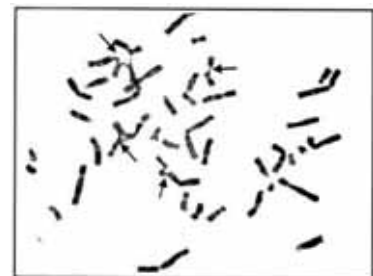
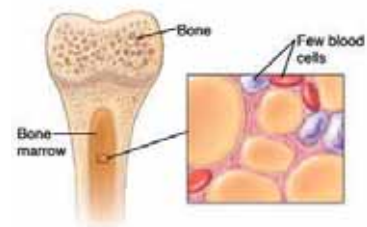
2. BM

- Hypo cellular BM
- Replaced by fibro fatty tissue.

3. In Fanconi anemia :

- Cytogenetic of blood lymphocytes shows increased chromosomal breakages and exchanges induced by mutagen (e.g. *Mitomycin C*)
- Mutation analysis

4. Investigations for a cause e.g. viral serology



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Differential diagnosis

- 1- From other causes of pancytopenia
- 2- From other causes of purpura e.g. Idiopathic thrombocytopenic purpura.

Treatment

1. Supportive care; see leukemia
2. Specific treatment: Indicated in severe aplastic anemia

a. For Fanconi anemia

1. Androgen therapy (Oxymetholone) effective in 50 %
2. Hematopoietic stem cell transplantation (HSCT) from HLA matched donor

b. For acquired aplastic anemia

1. Hematopoietic stem cell transplantation from HLA matched donor
2. If HSCT was unavailable use (alone or in combination):
 - Anti thymocyte globulin
 - Cyclosporine
 - Methyl prednisolone
 - Granulocyte colony stimulating factor (G-CSF)

Causes of pancytopenia:

- * Bone marrow failure e.g.
 - Aplastic anemia
 - Advanced megaloblastic anemia
 - Myelophthisis: Bone marrow infiltration
- * Hypersplenism (Pancytopenia with compensatory bone marrow hyperplasia)
- * Fulminant sepsis
- * Auto immune (Evans syndrome)

Congenital Pure red cell anemia

(Diamond Blackfan Anemia)

Definition

Familial disease due to decreased sensitivity of erythroid cells to erythropoietin → hypoplasia of RBCs precursors.

Clinical picture

- Pallor: usually evident by the 2nd – 6th months.
- Associated anomalies
 - Abnormal thumbs; (*triphalangeal thumb*)
 - Congenital heart diseases.
 - Short stature
- Hepatosplenomegaly, if present, is due to chronic transfusion therapy.
- High risk of acute myeloid leukemia.



Investigations

1. CBC

- Macrocytic anemia & reticulocytopenia
- Normal platelets and WBCs.
- Increased erythrocyte adenosine deaminase activity (ADA) & hemoglobin F

2. BM

- Decreased erythroid cells.
- Normal myeloid and megakaryocytic cells.

Treatment

- 1- Steroids: Give remission in 80%.
- 2- Chronic transfusion therapy **with** iron chelation for steroid resistant cases
- 3- Bone marrow transplantation.

Differential Diagnosis

Form acquired pure red cell anemia

* **Idiopathic: Transient erythroblastopenia of childhood;**

- Due to transient immunologic suppression of RBCs synthesis
- No anomalies
- Normocytic normochromic red cells
- Usually need no treatment (recover within 1-2 months).

* **Secondary:** to Drugs, Infections, Parvo B19, Malnutrition

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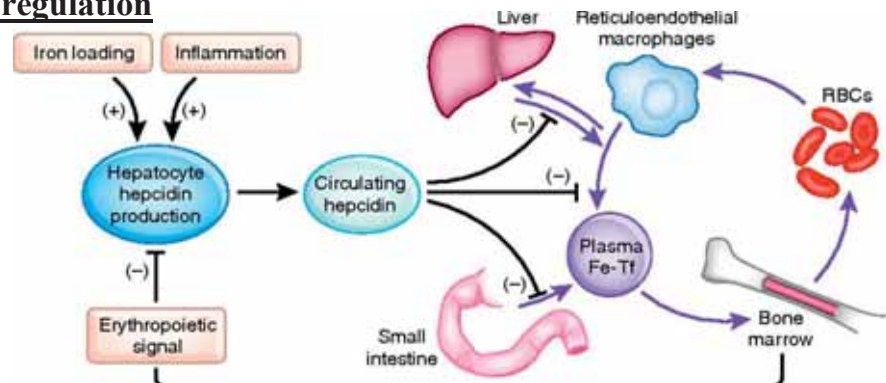
Iron Deficiency Anemia (IDA)

Incidence: The most common cause of anemia in pediatrics.

Iron metabolism

- Daily requirements: 8-15 mg/day
- Most of dietary iron present in ferric state.
- ⇓
- Iron changes to ferrous by combined action of HCL & vitamin C.
- Only **5-10%** of dietary iron is absorbed from the duodenum and proximal jejunum
- ⇓
- Factors enhancing absorption e.g. decreased hepcidin, vitamin C, ↑ erythropoiesis
- Factors impairing absorption e.g. increased hepcidin, hypochlorhydra, tannate
- ⇓
- Absorbed iron is bound to serum **transferrin** and stored as **ferritin** to be used in
 - a. In bone marrow → RBCs
 - b. In cell enzymes e.g. Catalase, peroxidase, mono amine oxidase (MAO).

Iron homeostasis regulation



- Hepcidin as the main regulator of systemic iron homeostasis
- Hepcidin synthesis is *induced* by iron loading and inflammation and *suppressed* by erythropoiesis.
- Increased hepcidin levels limit further enteral iron absorption and release of iron from the liver and the reticuloendothelial system to normalize plasma iron levels.
- With increased inflammation, elevated hepcidin levels cause the same sequence of events, leading to reticuloendothelial blockade and the anemia of inflammation.

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Causes

1. Decreased intake In infants 6-24 months due to:



- a. Delayed weaning (Prolonged breast-feeding without supplementation) due to:
- Depletion of the baby's iron store by the 6th month
 - Iron in breast milk is no more enough beyond 6th month



- b. Unfortified animal (Cow) milk feeder
Due to:
- Low iron content
 - Low lactoferrin content
 - Presence of heat labile protein which induces occult blood loss



2. Decreased iron absorption

- Excess tea, phytate & antiacids
- Achlorhydra e.g. atrophic gastritis
- Malabsorption syndrome

3. Decreased iron stores

- Iron deficient pregnant
- Perinatal blood loss.
- Preterm.



4. Increased loss

a. Occult blood loss due to

- Ankylostoma
- Cow milk protein allergy
- Drug induced gastritis.
- Peptic ulcer, polyps, GERD
- Meckle's diverticulum
- Esophageal varices

b. Overt blood loss e.g

Epistaxis, hematuria, hemodialysis



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5. Increased requirements due to:

- Accelerated rate of growth in preterm, infants, adolescence.
- Congenital cyanotic heart diseases (due to polycythemia)



Clinical picture

1. Mild anemia is asymptomatic.
2. Manifestations of anemia (anorexia, pallor,...) vary with severity of iron deficiency.

3. Systemic manifestations:

- Decreased Alertness, learning & concentration span (due to ↓ iron containing cellular enzymes).



- Palpitation (Tachy cardia) on exertion
- Cardiomegaly in severe deficiency



- Palpable spleen in about 10 % of cases
- Pica (Geophagia) desire to ingest unusual substances e.g. dirt, mud, chalk (increases the risk of concomitant lead poisoning)



- Atrophic glossitis : tongue is pale ,glazed (smooth)
- Angular stomatitis



- Nails ⇒ Brittle , longitudinal ridges, flattening and spooning (koilonychia)



4. Clinical signs of an underlying cause e.g. Ankylostoma anemia

Iron deficiency anemia plus

- Parotid enlargement (endemic parotitis)
- Recurrent abdominal Pain
- Bouts of diarrhea and constipation
- B complex vitamins deficiency: pellagra , nutritional edema
- Eosinophilia in the CBC and ova in stool analysis

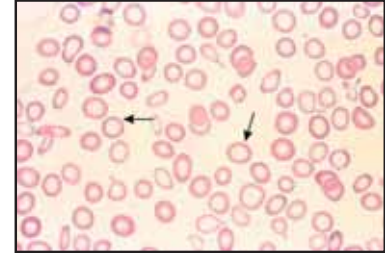
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Investigations

A. For diagnosis

1. CBC

- Anemia: ↓ Hb%, ↓ RBCs count
- Hypochromia: - MCH < 27 Pg
- MCHC < 30%
- Microcytosis MCV < 70 fl



* Blood film shows:

- Abnormally large central pallor (hypochromic cells)
- Target cells
- *Wide red cell distribution width (RDW)* and anisocytosis

* Normal white blood cells

* Thrombocytosis is often present

2. Iron indices

Index	Iron deficiency	normal range
○ Serum Iron.	< 30 µg / dl	60 - 140 µg / dl
○ Transferrin saturation.	< 16 %	30%
○ Total iron binding capacity (TIBC)	Increased	250-400µg / dl
○ Soluble serum transferrin receptors	Increased	Variable cutoff
▪ Serum ferritin (index of iron stores)	< 15 ng / ml	15-300 ng/ml
▪ Reticulocyte hemoglobin content *	< 27.5 pg	
▪ Marrow iron stores	Absent	
▪ Hepcidin **	Usually ≤10 ng/mL	

* A sensitive indicator that falls within days of onset of iron-deficient erythropoiesis and is unaffected by inflammation

** Extremely elevated in anemia of inflammation and suppressed in iron deficiency anemia

B. For the cause

- Stool analysis for parasites, ova and occult blood tests
- GIT barium study, endoscopy, and tests for achlorhydra
- Workup for malabsorption
- Workup for hemorrhagic diseases

Treatment

1. Treat the cause

2. Diet

- Excessive intake of milk, particularly bovine milk, should be limited
- infants who are breast and cow milk feeders require prophylactic oral iron given at 4th – 6th months (2mg/kg/d)
- in weaned; encourage intake of vitamin C, meat, fish

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3. Iron preparation

Oral Iron

- Dose: 3- 6 mg/kg/d. elemental iron
- In-between meals
- Continued for 8 wk after blood values normalize to re-establish iron stores
- Side effects: GIT upset, constipation and dark stool.
- Preparations:
 - Ferrous sulphate (The best; contain 20 % elemental iron)
 - Ferrous gluconate
 - Ferrous lactate

Parenteral Iron

- Preparation
 - Iron Dextran (Imferon) or Iron sucrose (Venofer) IV
 - Iron sorbitol (Jectofer) deep IM
- Indications
 - Intolerance to oral iron
 - GIT disorders aggravated by oral iron e.g. IBD
 - Malabsorption
 - Rapid loss of iron
- Side effects
 - With IM → staining, abscess
 - With IV → anaphylaxis (start with an observed test dose)

4. Packed red cell transfusion: is considered in

- Severe anemia (Hb < 7- 8 gm/dl).
- Anemic heart failure.
- Infection interfering with iron therapy.

Response to iron therapy

Time after iron administration	Response
By the 1 st day	Replaced cellular enzymes → decreased irritability and improved appetite.
By the 2 nd day	Erythroid hyperplasia in bone marrow.
By the 3 rd day	Reticulocytosis peaking at 5-7days
By the 1 st month	Increase hemoglobin at rate of 0.25 – 0.5 gm/dl/day
By the 3 rd - 6 th months	Repletion of stores.

Mentzer index (MI) = Packed cell volume / RBC count in millions

* Help differentiate microcytic anemia of iron deficiency from β thalassemia trait

* MI In iron deficiency anemia >13 * MI In β thalassemia trait <13

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Differential Diagnosis of microcytic anemia that fails to respond to oral iron

1. Poor compliance / incorrect dose or medication
2. Malabsorption of administered iron
3. Ongoing blood loss
4. Concurrent infection or inflammatory disorder inhibiting the response to iron
5. Concurrent vitamin B₁₂ or folate deficiency
6. **Diagnosis other than iron deficiency**
 - a) **Hemoglobinopathies:** Thalassemia , Sickle thalassemia , Hemoglobin C and hemoglobin SC disease
 - b) **Anemia of chronic disease**
 - In any disease with chronic inflammation e.g. Chronic infections
 - Anemia is usually normocytic ; occasionally microcytic
 - Inflammatory mediators and raised Hepcidin are the main etiologies
 - c) **Lead poisoning**
 - History of exposure or iron deficiency with Pica
 - Blue staining of gums, abdominal pain
 - Lab: Basophilic stippling of RBCs ,high serum lead level, free erythrocyte protoporphyrin
 - d) **Siderblastic anemia** (X-linked disorder)
 - Due to abnormal erythrocytic 5-aminolevulinic acid synthetase (ALAS), the rate-limiting enzyme reaction in heme synthesis. An important cofactor for ALAS is pyridoxal phosphate.
 - Treatment: Stem cell transplantation for transfusion dependent cases

	IDA	Anemia Of Chronic Disease	Thalassemia traits	Sideroblastic Anemia
Serum Ferritin	– Decreased	– Increased	– Normal	– Increased
Serum iron	– Decreased	– Decreased	– Normal	– Increased
TIBC	– Increased	– Decreased	– Normal	– Normal
Transferrin saturation	– Decreased	– Decreased	– Normal	– Increased
Bone Marrow	– Absent iron	– Increased iron	– Normal iron	– Increased iron – Ringed sideroblasts
Specific	– ↑↑ Soluble transferrin receptors – ↓↓ Hepcidin	– Normal soluble transferrin receptors – ↑↑ Hepcidin – High CRP	– Electrophoresis	– HSM, icterus – May respond to B6

(Nelson textbook of pediatric)

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Megaloblastic anemia

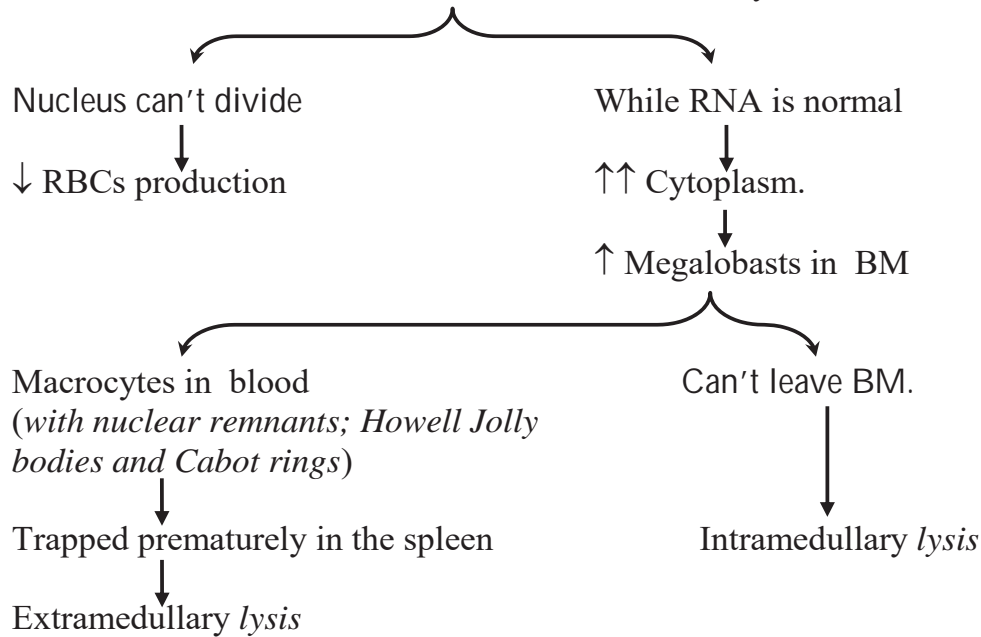
Definition: Anemia with megaloblasts in BM and macrocytes in peripheral blood.

Causes

- i- Vitamin B₁₂ (cobalamin) deficiency
- ii- Folic Acid deficiency.

Pathogenesis

Folic acid & B₁₂ are essential for DNA synthesis in stem cells of RBCs, platelets and WBCs. So in folic acid or B₁₂ deficiency



Metabolism

Vitamin B ₁₂	Folic acid
Sources Animal origin only e.g. milk, meat.	- Animal & plant (green leaves, fruits)
Requirements 5 – 20 µg /day	20 – 50 µg /day
Absorption Gastric parietal cells release intrinsic factor (IF) which binds to B ₁₂ → B ₁₂ /IF complex → absorbed from the terminal ileum	Absorbed from the proximal intestine (duodenum and jejunum) Requires vitamin C for absorption
Stores enough for 2-4 years	Stores enough for 2-4 months

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Causes of B₁₂ and folic acid deficiency

	Vitamin B ₁₂	Folic acid
Decreased intake	* Infants breast fed to vegetarian mums	* Infants fed on: Goat's milk
Decreased absorption	* Malabsorption syndrome * Intrinsic factor defect - Pernicious anemia - Gastrectomy * B ₁₂ /IF consumption by <i>Diphyllobothrium latum</i> or bacterial overgrowth. * Ileal disease Or resection	* Malabsorption syndrome * Vitamin C deficiency
Impaired metabolism	Defective transport: Transcobalamin II deficiency	* Cytotoxic drugs → methotrexate * Anticonvulsant → phenytoin → valproate
Others	.	* Increase requirements: e.g. - Prematures (↓stores) - Pregnancy - Chronic Hemolytic anemia * Reduced stores: liver cirrhosis * Increased loss: hemodialysis

Clinical picture**A. Hematologic**

- * Anemia (Anorexia, pallor, *tiredness* ,) with slight jaundice.
- * Advanced megaloblastic anemia → thrombocytopenic purpura and leucopenia
- * Mild hepatosplenomegaly due to intramedullary hemolysis

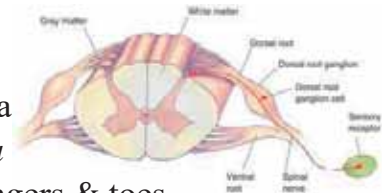
B. GIT manifestations esp. in folate deficiency:

- * Atrophic glossitis → Beefy red glazed tongue in 25 %
- * Atrophic gastritis → Dyspepsia, vomiting, risk of cancer stomach
- * Atrophy of intestinal mucosa → Abdominal pain and chronic diarrhea.

**C. Neurologic manifestations: Sub acute Combined Degeneration (SCD)**

Only with severe vitamin B₁₂ deficiency (? irreversible)

- * Degeneration of
 - Posterior column → deep sensory loss, sensory ataxia
 - Pyramidal tract → Progressive *weakness*, *Paraplegia*
 - Peripheral Nerve → Symmetrical paraesthesiae in fingers & toes

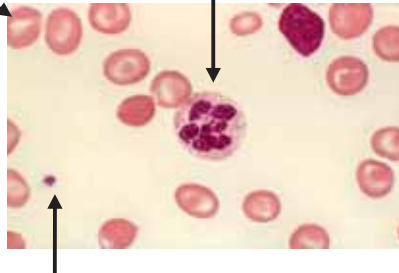


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Diagnosis**1. Is it megaloblastic anemia?****CBC****Macrocytic anemia**

- Low Hb% & Ht value
- MCV > 100 fl
- MCHC = normal

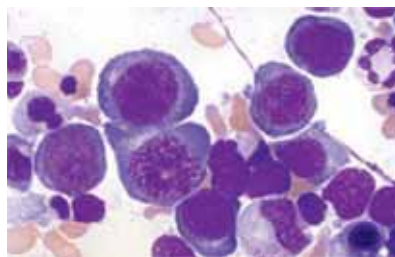
Hyper segmented (hyper mature) neutrophils (contain 4-5 lobes).



Thrombocytopenia, leucopenia and reticulocytopenia in advanced cases.

BM

- Erythroid hyperplasia
- Megaloblastic changes

**2. What is the cause?****A. Vitamin B₁₂ deficiency****i. Is there Vitamin B₁₂ deficiency?**

- Low serum vitamin B₁₂ (Diagnostic)
- Therapeutic test: 1 µg B₁₂ → reticulocytosis at 6th day

ii. What is the cause of Vitamin B₁₂ deficiency?**a. Schilling test:** done if the etiology was unclear

Radioactive B₁₂ is given orally followed by an I.M. injection of non-radioactive B₁₂ to saturate B₁₂ binding proteins

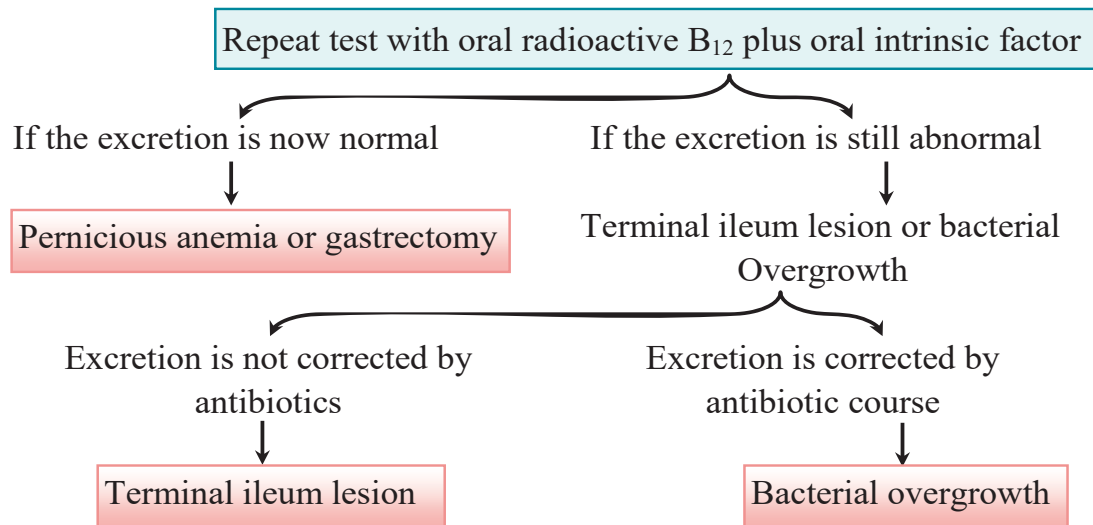
Normally

>10 % of oral B₁₂ excreted in urine

If this is abnormal

The test is repeated with the addition of oral intrinsic factor capsules

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b. Gastric function tests: Histamine or pentagastin test confirm achlorhydria

c. Serological tests: Anti-parietal and anti-IF antibodies

B. Folic acid deficiency

* Low serum folate; RBC level is better measure of tissue folate (Diagnostic)

* Therapeutic test: 0.2 mg Folate → look for reticulocytosis at 6th day

Treatment

A. B12 deficiency

a. Pernicious anemia

- Hydroxocobalamin IM 1000 µg to a total of 6 mg over the course of 3 weeks Then 1000 µg every 3 months for the rest of the patient's life.
- Recent alternatives: high oral or sublingual dose 2 mg per day

b. Gastrectomy or ileal disease:

Monitor serum B₁₂ → whenever low → give prophylactic vitamin B₁₂

c. Treat the underlying disease

B. Folic acid deficiency

a. Treat the underlying disease

b. Exclude subclinical B₁₂ deficiency which can be aggravated by folic acid therapy

c. Folic acid 5 mg/day continued for 4 months to replace body stores.

d. Prophylaxis

- Chronic hemolytic anemia 5 mg weekly
- Premature < 1500 gm require 1 mg daily for 6 weeks

N.B:

Folic acid may produce a hematological response in vitamin B₁₂ deficiency but may aggravate the neuropathy. So Large doses of folic acid alone should not be used to treat megaloblastic anemia unless the serum vitamin B₁₂ level is known to be normal

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Hemolytic Anemia

Definition

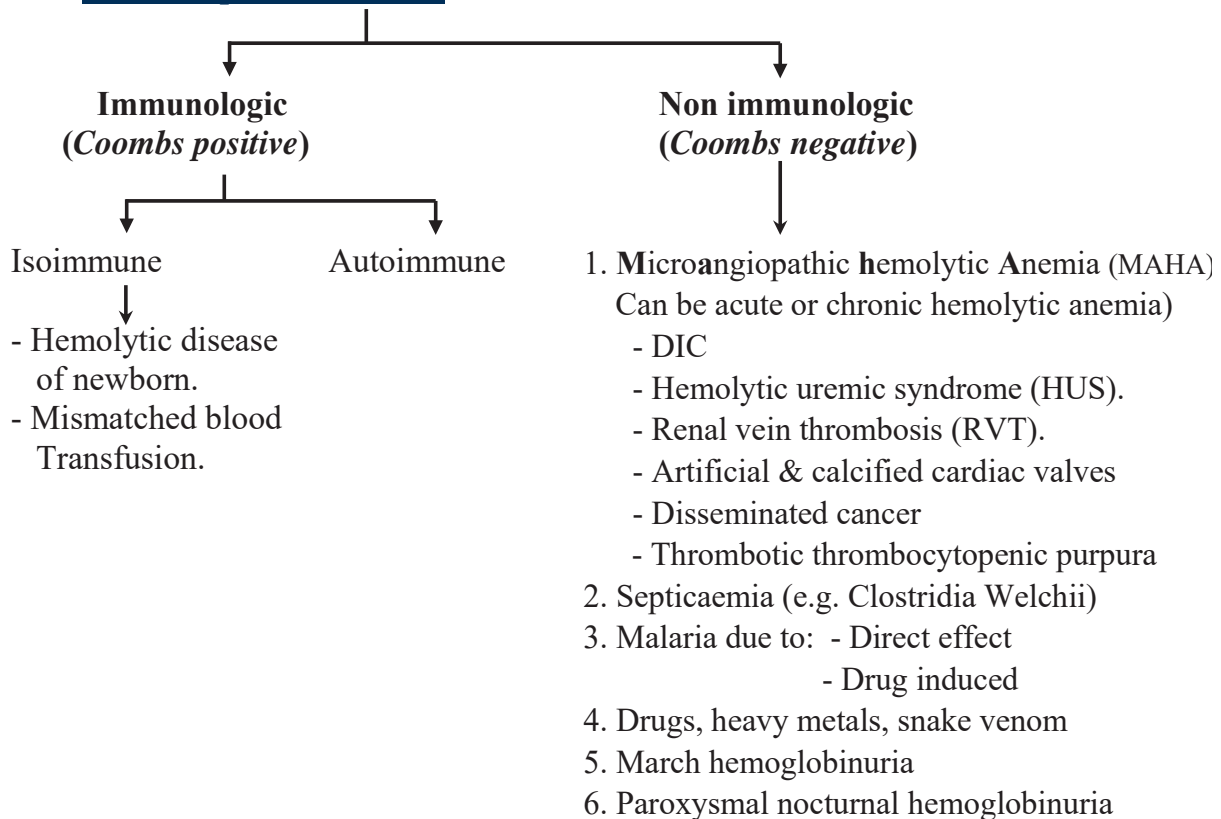
- Anemia resulting from increased RBCs destruction exceeding bone marrow capacity for compensation (reduced RBCs survival).
- Normal RBCs life span 120 days.

Acute Hemolytic Anemia (Intra vascular hemolytic anemia)

Causes

A. Intra corpuscular causes: - Enzymatic defects e.g. G6PD deficiency

B. Extra corpuscular causes



General clinical manifestations

- Acute pallor.
- HyperBilirubinemia:
 - Indirect; lemon yellow color
 - Dark colored urine (*hemoglobinuria*)
- Pyrexia and rigors.
- Loin Pain.
- In Profound anemia: rapid decompensation with blurred vision, lassitude and anemic heart failure even death

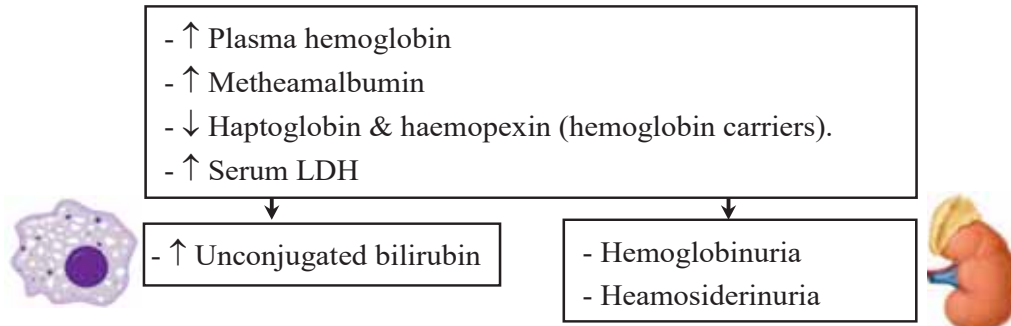


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General workup

1. **Anemia:** Usually normocytic normochromic , low Hb% and Ht. value.

2. **Decreased RBCs Survival** indicated by:



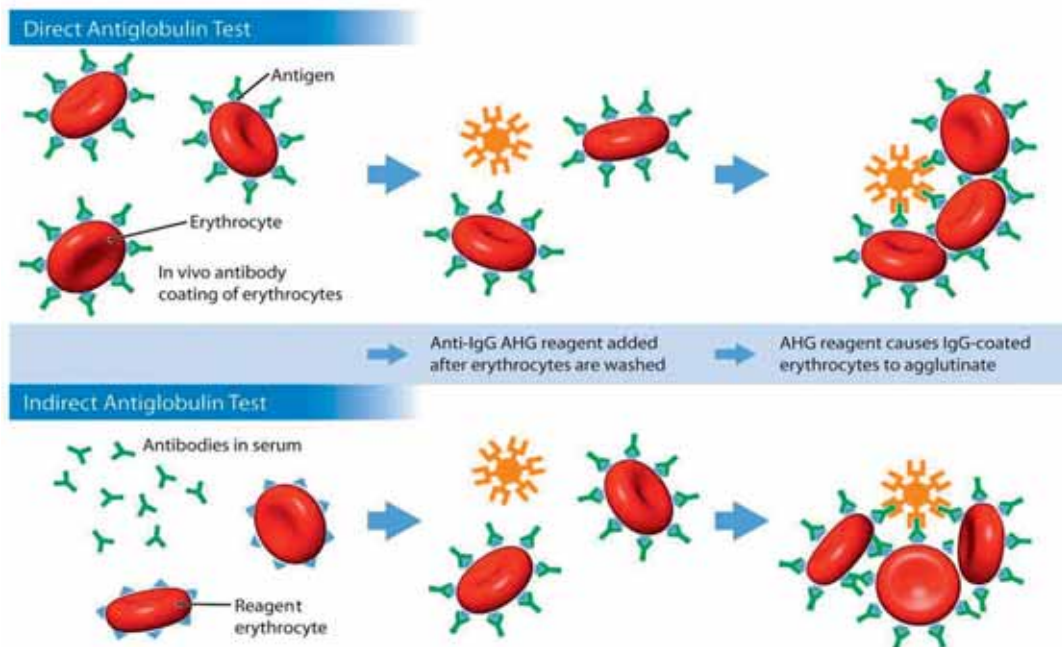
3. **Increased erythropoiesis** indicated in the CBC by:

- Reticulocytosis: Reticulocytic count > 8%
- ↑ Normoblasts (immature nucleated RBCs).

Specific investigations

1. **Coombs test (Anti Globulin Test):** Diagnose Immunologic hemolytic anemia.

- Direct Coombs test detect antibody coated RBCs
- Indirect Coombs test detect free antibodies in serum



2. **Blood film for:**

- Heinz bodies in G6PD deficiency.
- Microangiopathic hemolytic anemia: - Fragmented RBCs (schistocytes).
- Thrombocytopenia.
- Malaria.

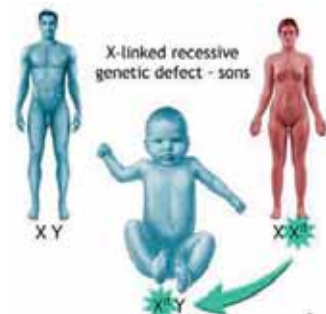
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Glucose - 6 - Phosphate Dehydrogenase Deficiency

(G6PD Deficiency)

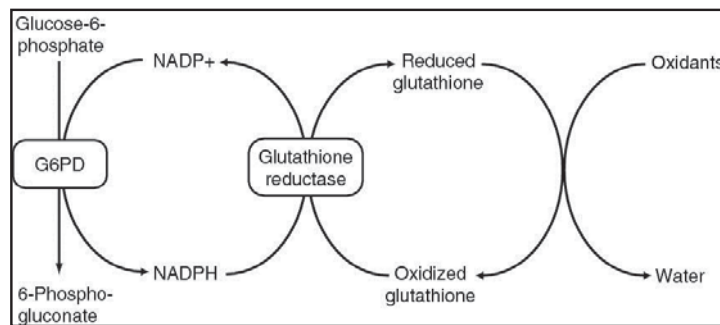
Etiology

- * Hemolytic anemia due to *age labile* Glucose - 6 - Phosphate Dehydrogenase enzyme
- * Sex linked recessive disorder which seen mainly in males
- * Occasionally seen in females if in homozygous state or heterozygous state with random inactivation of the other normal X chromosome (Lyon hypothesis).



Pathogenesis

- * G6PD enzyme is key enzyme of Hexose Mono Phosphate (HMP) shunt which produce reduced glutathione.
- * Reduced glutathione protects the red cells against oxidizing agents.



- * In G6PD deficiency → ↓ reduced glutathione → impaired elimination of oxidants → oxidation of Hb → methemoglobin → precipitate inside RBCs → acute hemolysis.

Oxidizing agents include

- Food → Fava beans (favism) contain *vicine* and *convicine* oxidants
- Infections → Viral or bacterial
- Drugs → Anti pyretics e.g. - Acetylsalicylic acid
- Phenacetin
→ Anti-microbial e.g.- Sulpha, Chloramphenicol, Nitrofurantoin
→ Anti-malarial e.g. Primaquine
→ Anti tuberculous e.g. Para amino salicylic acid, isoniazid



Genetic variants

- Types A⁺ & B⁺ → Normal variants.
- Type A⁻ → American type (enzyme activity = 5-15%).
- Mediterranean type → Severe deficiency (enzyme activity < 5%).
- Canton type.

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Clinical picture

A. Acute hemolytic anemia

- Features of acute hemolysis without organomegaly (*see before*).
- Occur 2- 3 days after exposure to the oxidant trigger.
- Degree of hemolysis varies with the triggering agent and the severity of G6PD enzyme deficiency
- Episodes usually brief as newly produced young RBCs have a higher enzyme activity that can withstand oxidant stress
- May occur in the neonatal period → neonatal anemia & jaundice.

B. Chronic non spherocytic hemolytic anemia

- Extremely rare.
- Presents with pallor, tinge of jaundice and mild splenomegaly.

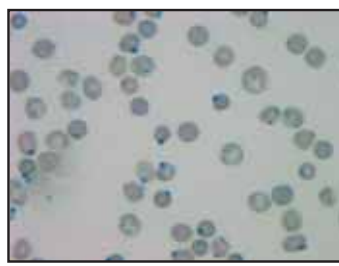
Investigations

1. For **anemia** → Low Hb% and Ht value.
2. For **acute hemolysis** → Evidence of ↓ RBCs survival and ↑ Erythropoiesis.
3. For **the cause**:

i. Blood film



- Fragmented RBCs
- Reticulocytosis



Heinz bodies

- Denatured hemoglobin
- Appear as purple blue intracellular inclusion bodies visible with supravital stains

ii. G6PD Enzyme assay

- Done few weeks (2-4 weeks) after the acute attack
- During the acute attack, the bone marrow produces young RBCs with higher enzymatic activity which may give false normal results.

Treatment

A. During the attack

- Resuscitation: Ensure ABC
- Packed RBCs transfusion (5-10 ml/kg) for severe attack (Hb < 7 gm/dl or < 9 gm/dl with persistent hemoglobinuria). Can be repeated
- Control triggers e.g. infection, stop oxidant agent
- In a neonate: treatment of associated neonatal jaundice



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B. After the attack

- Avoid oxidant food & drugs.
- Anti oxidant → vitamin E.
- Offer screening of other sibling boys
- Offer a *card* with diagnosis that include forbidden and alternative drugs (e.g. Anti pyretics in fever → paracetamol **or** ibuprofen) and avoided foods

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Chronic Hemolytic Anemia

Causes

A. Intra corpuscular causes

1. Membrane defects
 - Hereditary spherocytosis
 - Hereditary elliptocytosis (ovalocytosis)
2. Hemoglobinopathy
 - α thalassemia
 - β thalassemia.
 - Sickle cell disease
3. Enzymatic defects
 - Pyruvate kinase deficiency

B. Extra corpuscular causes

1. Immunologic (Coombs +ve): Autoimmune hemolytic anemia (Warm type)
2. Non immunologic (Coombs -ve): Hypersplenism

General clinical features

a. Initially

1. Features of progressive Anemia (pallor, fatigue,...)
2. Tinge of jaundice :
 - Indirect hyperBilirubinemia ; lemon yellow color
 - Normal colored urine (acholuric jaundice)



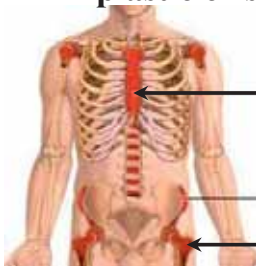
b. In advanced and neglected cases

1. Skeletal changes due to bone marrow expansion:
 - * Head (Mongloid features):
 - Macrocephaly.
 - Depressed nasal bridge.
 - Prominent maxillae.
 - Prognathism.
 - * Generalized osteoporosis.
2. Splenohepatomegaly due to extramedullary hematopoiesis & hemosiderosis
3. Gall bladder Stones (Calcium bilirubinate) in chronic hemolysis for > 4 years.



c. Hematologic crises

1. **Aplastic crisis** (*Erythroblastopenic crisis*)



- Transient bone marrow hypoplasia
- Due to parvo-B19 infection (infect erythroid cells).
- Clinically:
 - Increased pallor without deepening of jaundice
 - Reticulocytopenia

2. **Megaloblastic crisis** due to folate deficiency → aggravation of anemia
3. **Hemolytic crisis**
 - Increased rate of hemolysis precipitated by infection
 - Increasing pallor, jaundice , reticulocytic count
 - Hemoglobinuria
4. **Hyperhemolytic crisis** due to associated G6PD deficiency

General Investigations

1. Anemia

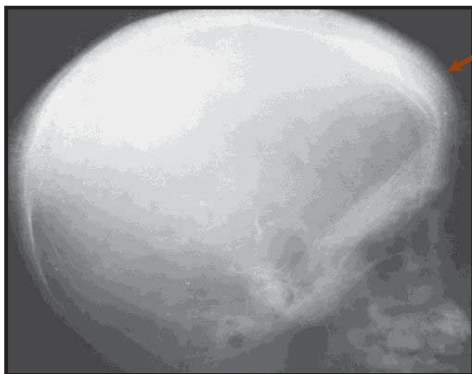
- * Low Hb% and Ht value
- * Usually normocytic normochromic but may be:
 - Macrocytic due to associated folate deficiency or marked reticulocytosis
 - Microcytic in thalassemia and chronic hemoglobinuria

2. Decreased RBCs survival

- * ↑ Unconjugated bilirubin (usually < 5 mg/dl)
- * Iron buildup: ↑ Serum iron and ferritin

3. Increased erythropoiesis

- * Modest reticulocytosis ; peaks in hemolytic and hyperhemolytic crises
- * **Skull X-ray:** shows



(Hair on end appearance).

- Marrow space expansion
- Wide diploic space
- Macrocephally

- * **Bone marrow aspirate:** shows

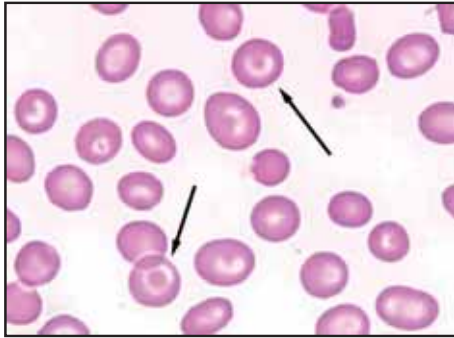


- Erythroid hyperplasia
- May be megaloblastic in associated folate deficiency
- May be aplastic in aplastic crisis or PNH

4. ↓ Chromium (⁵¹Cr) labelled RBCs survival:

Direct evidence of short RBCs survival (research tool only)

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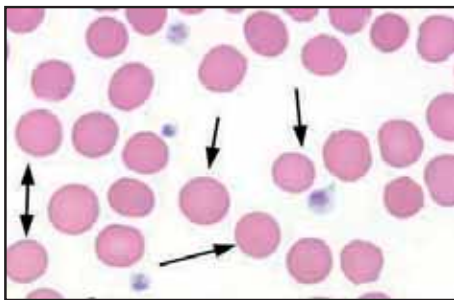
Specific investigation**1. Coombs test:** Diagnose Immunologic hemolytic anemia.**2. Blood film** for abnormal RBCs morphology e.g.**a. Target cells**

RBCs with central staining, a ring of pallor, and an outer rim of staining seen in

- Thalassemia
- Sickle cell disease
- Hyposplenism
- Obstructive liver disease
- Iron-deficiency anemia

**b. Sickle cells**

Seen in sickle cell anemia

**c. Microspherocytes**

Small spherical cells with loss of central pallor , Seen in

- Hereditary spherocytosis
- Immune hemolytic anemia
- Hypersplenism
- Burn
- Sickle Cell disease

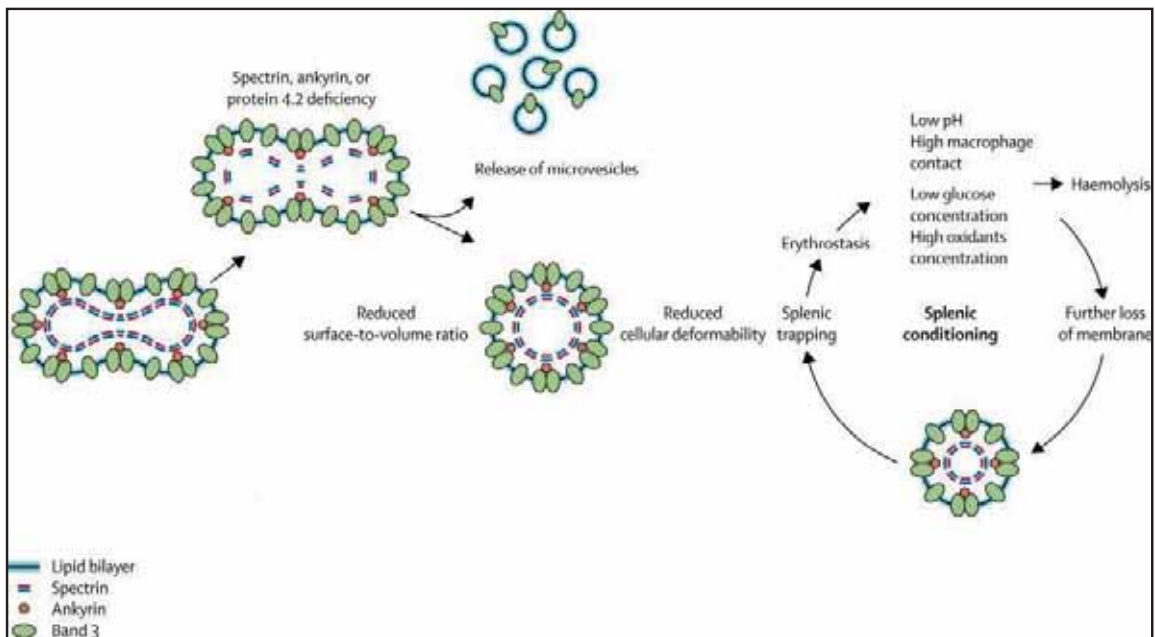
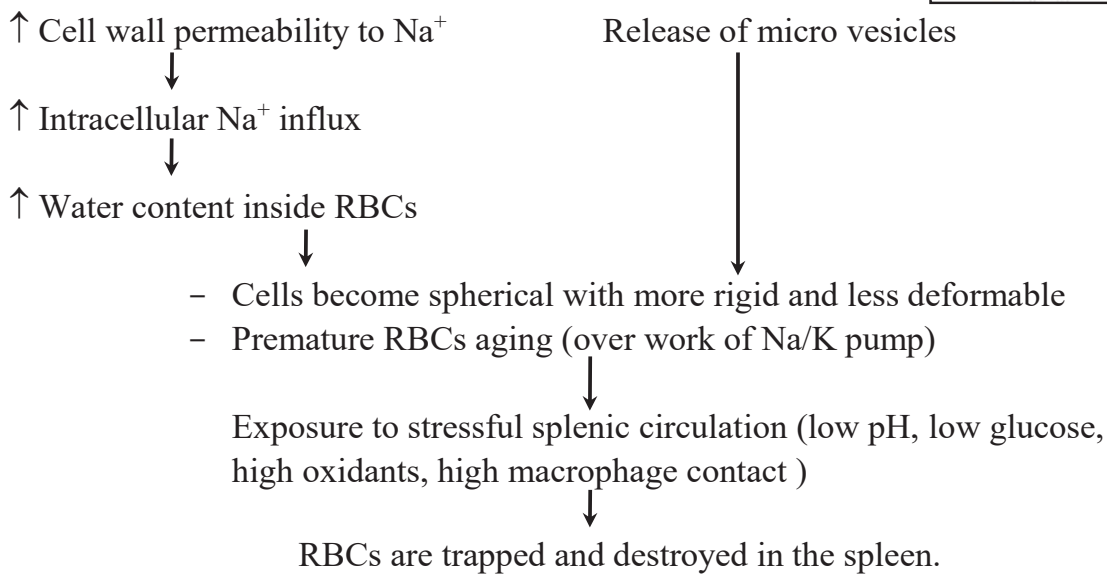
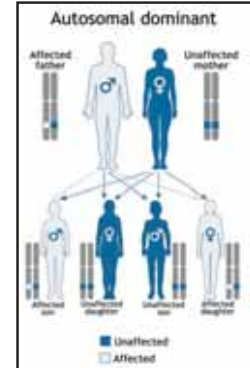
3. Osmotic fragility test/auto hemolysis test for Hereditary spherocytosis**4. Flow cytometry** for PNH (Ham test is no longer used)**5. Hb electrophoresis** for hemoglobinopathies

Hereditary Spherocytosis

(Familial acholuric jaundice)

Pathogenesis

- The most common inherited hemolytic anemia in northern Europeans
- Autosomal dominant disorder
- Due to deficiency of red cell cytoskeleton proteins (Ankyrin or Spectrin or protein 4.2)



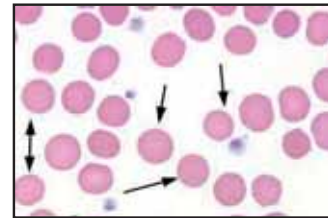
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Clinical picture

- * Some patients may go through life with no symptoms
 - * Positive family history is present in **75%** of symptomatic cases
 - 1- Features of anemia
 - 2- Features of chronic hemolysis
 - 3- Gall stones are seen in **50%** of unsplenctomized cases by 4-5 years
- } starting early in life; **50%** present by neonatal anemia and jaundice.

Investigations

1. For **anemia** → ↓Hb% and ↓Ht value (usually normocytic anemia)
2. For **chronic hemolysis** → ↓ RBCs survival & ↑ erythropoiesis.
3. For **the cause**:
 - a. Blood film → RBCs are small, rounded without central pallor i.e. spherocytes.
 - b. Negative Coombs' test rules out autoimmune hemolytic anemia as a cause of spherocytes in blood film.
 - c. Incubated osmotic fragility test:
 - Test is non-specific ;miss up to 20% of cases
 - Normally when red cells are placed in solutions of increasing hypotonicity, it takes in water, swell, and eventually lyses.
 - Spherocytes (already swollen cells) lyse more readily than normal biconcave cells
 - In equivocal results ; perform *incubated osmotic fragility test* (incubate for 24 hours at 37 °C)
 - Hemolysis is partially corrected by addition of glucose
 - d. Flow cytometric EMA (Eosin-5- Maleimide) binding test **and** the cryohemolysis test are much more sensitive and specific



The diagnosis of HS can be established from:

1. A positive family history and
 2. The presence of typical clinical and laboratory features of the disease: splenomegaly, spherocytes on the blood smear, reticulocytosis, and an elevated mean corpuscular hemoglobin concentration.
- If these are present, no additional testing is necessary to confirm the diagnosis.
 - If the diagnosis is less certain, the recommended tests that have a high predictive value for HS are the flow cytometric EMA (eosin-5- maleimide) binding test and the cryohemolysis test
- (Nelson textbook)

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Medical treatment

- 1- Supportive → folic acid 1mg/day (till splenectomy is done)
- 2- Slight anemia (Hb > 10 gm/dl & reticulocytic count < 10%) → follow up
- 3- Severe anemia requires packed red cells transfusions.

Elective splenectomy:

- Indications** → Moderate to Severe anemia
 → Frequent crises
 → Poor growth
 → Cardiomegaly
- Value** : Clinical cure → prevent hemolysis, crises and gall bladder stones
- Timing** : It is best to postpone splenectomy until after 6 years to avoid overwhelming fatal infections
- Risks** : Increased risk of overwhelming infections, particularly encapsulated organisms
- Precautions** A. Vaccinate 2–3 weeks before splenectomy for:
- Pneumococcal polysaccharide vaccine; repeated every 5 years
 - Meningococcal group C vaccine
 - Influenza vaccine; repeated annually
 - Haemophilus influenzae type B (Hib) vaccine
- B. Long-term penicillin V 250mg 12-hourly (or erythromycin)
- C. Aggressive treatment for any febrile illness

N.B: Often, concomitant cholecystectomy should be performed if there are gallstones detected in pre-operative abdominal ultrasound.

Paroxysmal Nocturnal Hemoglobinuria

Etiology

- * Acquired hemolytic anemia where RBCs are susceptible for complement damage
- * Hematopoietic stems cells membranes lack decay accelerating factor (CD55) and CD59 which are involved in complement degradation
- * Absence of CD55 and CD59 → uncontrolled hemolytic action of complement
- * Anemia is chronic with acute exacerbations

Clinical picture

- * Features of intravascular hemolytic anemia with hemoglobinuria especially after sleep by night
- * Attacks of abdominal and back pain due to micro thrombi
- * Complications
 - Venous thrombosis
 - Iron deficiency
 - Aplastic anemia

Investigations

A. General investigations for intravascular hemolysis

B. Specific: Flow cytometric analysis of red cells with anti-CD55 and anti-CD59

Treatment

1. Blood transfusions (Leucocyte-depleted blood to prevent transfusion reactions)
2. Eculizumab
 - A recombinant humanized monoclonal antibody that prevents the cleavage of C5 (and therefore the formation of the membrane attack complex).
 - It reduces intravascular hemolysis, hemoglobinuria, the need for transfusion
 - Given IV every 2weeks
 - Very expensive
3. Long-term anti-coagulant prophylaxis for patients with deep venous thrombosis
4. Folic acid 3mg daily
5. Bone marrow transplantation

Thalassemia

Definition: Autosomal recessive disorders due to defective globin chain production

A. α thalassemia syndromes

- ✧ Impaired α chain production
- ✧ Due to deletion of one or more of the 4 α globin genes on chromosome 16

1. One gene missing → Silent carrier (Asymptomatic)

2. Two gene missing → α thalassemia trait

- Familial microcytic anemia ; commonly mistaken as iron deficiency
- Normal iron indices
- Normal Electrophoresis for age.
- Diagnosed by DNA analysis.

3. Three genes missing → Hemoglobin H disease

- Mild to moderate microcytic hemolytic anemia at birth
- Evidence of chronic hemolysis
- Electrophoresis shows: Hb H (4 β chains).

4. Four genes missing → Fetal hydropes

- Severe intra uterine anemia and anemic heart failure
- Resulting in death in-utero or short after birth
- Electrophoresis shows: Dominant hemoglobin Bart (4 γ globin chains) with complete absence of normal fetal and adult hemoglobin

B. β -thalassemia syndromes

- Impaired β chains production
- Due to mutation of one or more of the 2 β globin genes on chromosome 11

A. One gene mutation → β thalassemia trait (Heterozygous β -thalassemia)

- Microcytic anemia with no evidence of overt hemolysis
- Differentiated from iron deficiency anemia by
 - Normal iron indices and Mentzer index <13
 - Characteristic hemoglobin electrophoresis:
 - Hb A₂ up to 3-7% in over 90% of cases.(diagnostic)
 - HbF up to 1-3% in only 50% of cases.

B. Two genes mutation → β thalassemia major

C. Thalassemia intermedia

- Due to a combination of homozygous mild β and α thalassemia
- Moderate anemia (Hb 7–10 g/dL) doesn't require regular transfusions

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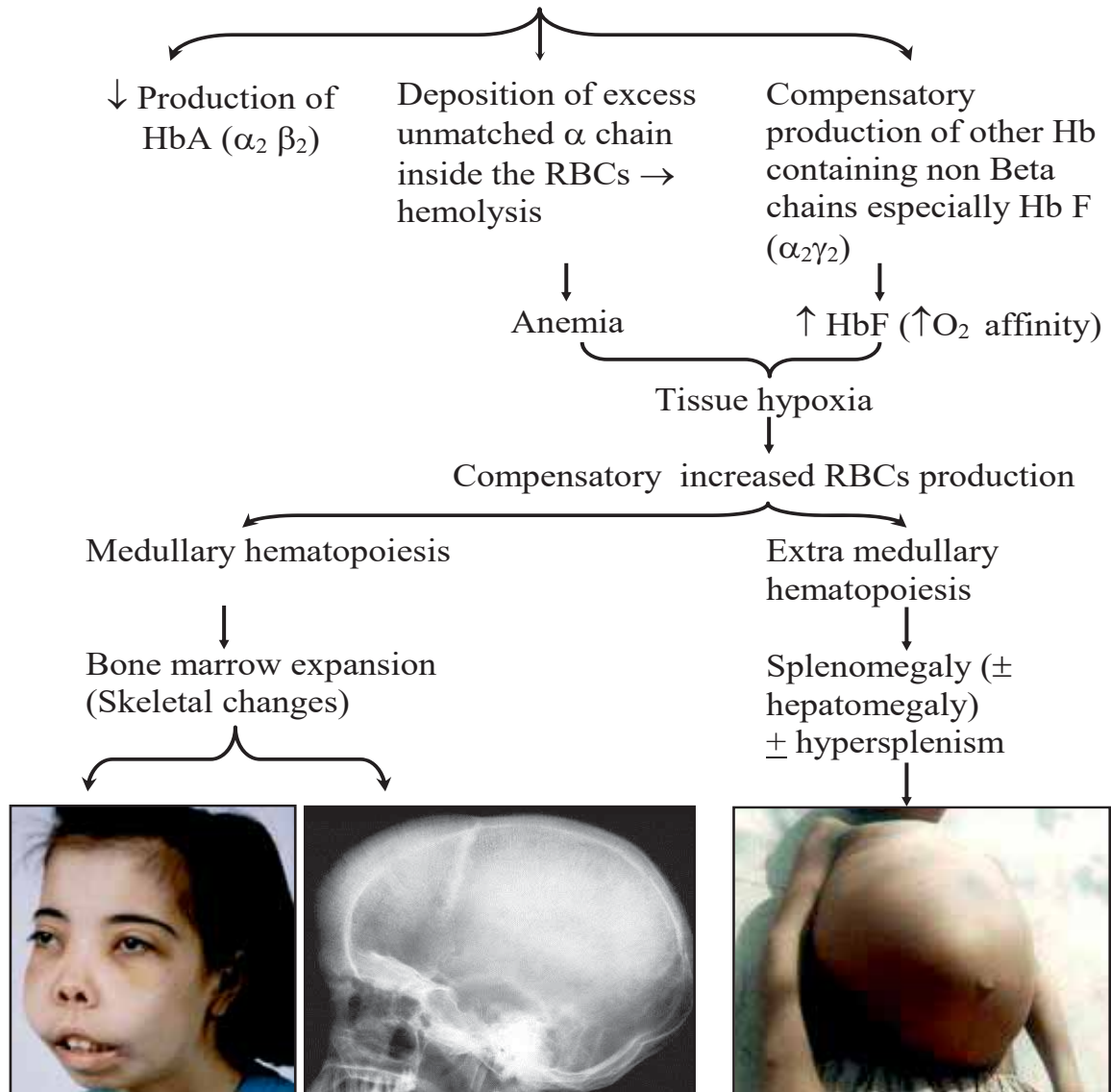
β Thalassemia Major

(Cooley's anemia)

The commonest chronic hemolytic anemia in Egypt & Mediterranean areas.

Pathophysiology

A. Impaired β chain production



B. Iron overload due to

- Chronic hemolysis.
- Enhanced iron absorption.
- Repeated blood transfusion.

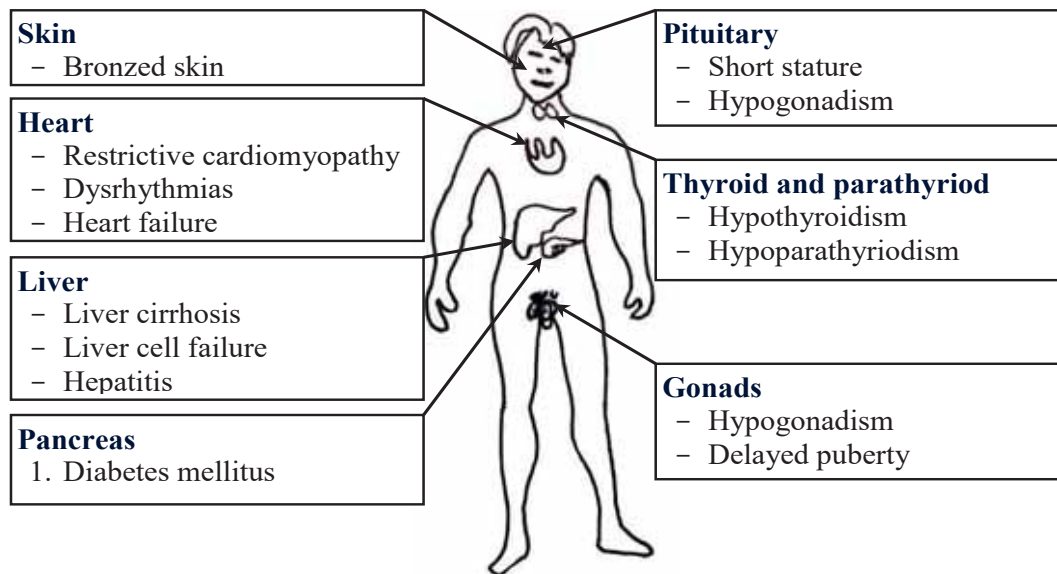
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Clinical picture

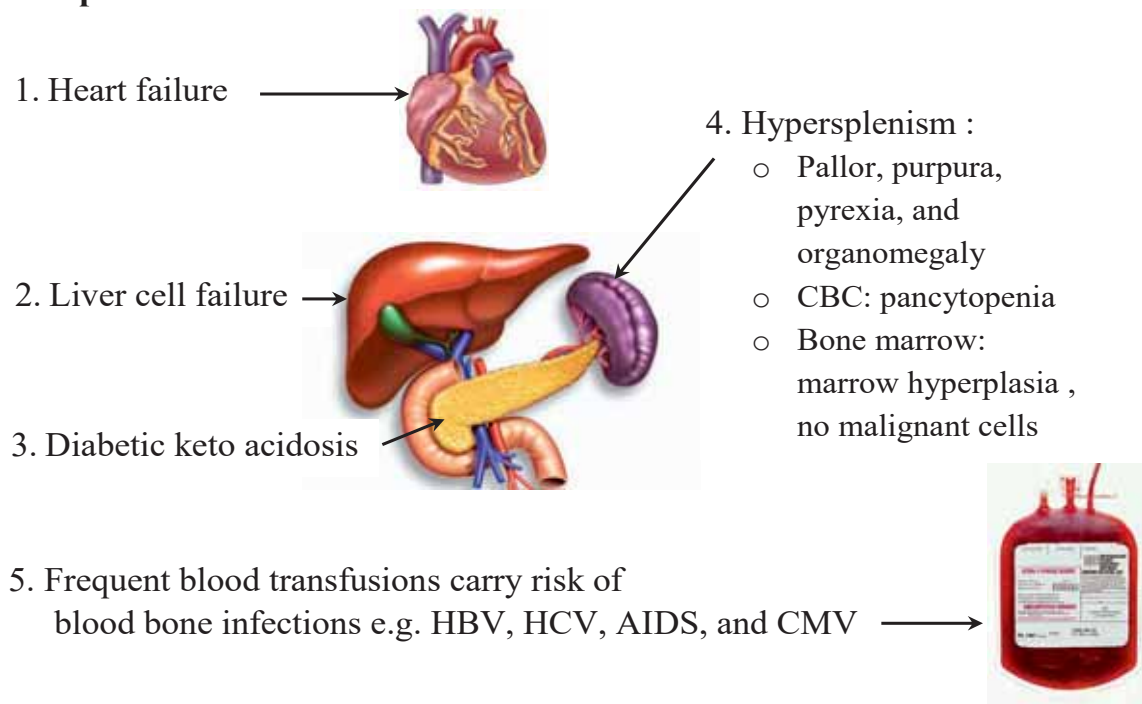
A. General features of *chronic hemolytic anemia* (see before)

- Manifestations start insidiously after the 6th month of age when switch from γ to β chain production usually normally occur.
- Classic features: Progressive anemia, jaundice, thalassemic facies, and organomegaly

B. Hemosiderosis → Iron deposition in:



C. Complications and causes of death



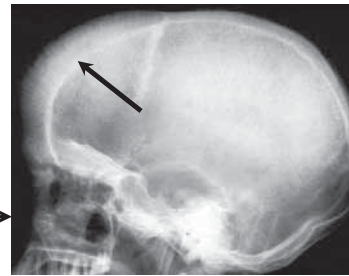
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Investigations

a. For anemia → Low Hb% and Ht. value.

b. For chronic hemolysis

- Unconjugated hyperbilirubinemia
- Reticulocytosis (commonly <8%)
- Skull X-ray in children >3 years →



"Hair on end" appearance

c. For the cause

- 1- Blood film → hypochromic, microcytic anemia with target cells.
- 2- Alkaline denaturation (Apt) test → Hb F resist denaturation by alkali
- 3- Hemoglobin electrophoresis:
 - Markedly raised Hb F (80-90%)
 - Slightly raised Hb A₂
 - Absent or near absent Hb A
- 4- Prenatal diagnosis is possible by chorionic villous sampling (CVS)

d. For diagnosis of iron overload

- Serum iron and ferritin
- Cardiac / hepatic MRI*
- Liver biopsy*
- Liver iron by Superconducting Quantum Interference Device (SQUID)

Treatment

1. Chronic transfusion therapy

- Indications for initiation of regular red cell transfusions include:
 - Hemoglobin level ,7 g/dl (on at least 2 measurements)
 - Poor growth
 - Facial bone changes
- Aim: To keep pre transfusion Hb > 9.5- 10.5 gm/dl
- Dose: 10-15 ml/kg packed RBCs monthly.
- Benefits
 - Allow normal growth and activity
 - Decreases bone marrow activity → ↓ skeletal changes.
 - Decreases extra medullary hematopoiesis → ↓ organomegaly.

2. Iron chelation therapy

- Often deferred until age 3 to 4 years.
- Indications:
 - Cumulative transfusion load of 120 ml/kg or greater
 - Serum ferritin level persistently >1,000 ng/ml
 - Liver iron concentration .5–7 mg/g dry weight

- **Drugs used**

- A. Desferrioxamine (Desferal)**

- Dose: 25-50 mg/kg/day
 - Route: IV or by continuous SC pump for 10 hours, 5-6 nights per week.
 - Side effect: anaphylaxis, deafness, cataract, retinal damage , yerssinia sepsis and skeletal changes
 - Ascorbic acid 200 mg daily enhance the chelating effect of Desferal

- B. Recent Oral drugs**

- 1. Deferiprone (Ferriprox)**

- Dose : 75-100 mg/kg
 - Value: Effective in Reducing cardiac iron overload.
 - Side effects: Gastric upset ,neutropenia and agranylocytosis

- 2. Defrasirox (Exjade)**

- As effective as desferal but oral with longer half life
 - Once daily, 20-40 mg /kg
 - Monitoring of liver enzymes and serum creatinine is essential

- 3. Supportive treatment**

- Low iron diet
 - Folic acid 1mg/day
 - Endocrine support as necessary.
 - Hepatitis A and B vaccine

- 4. Splenectomy**

- Indications

- A. Hypersplenism suggested by:

- Increasing need for transfusion by $\geq 50\%$ than usual for > 6 months.
 - Annual PRBCs > 250 ml/kg/year in face of uncontrolled iron overload
 - Severe leucopenia and / or thrombocytopenia (Pancytopenia)

- B. Huge spleen with pain or pressure symptoms.

- When: Preferably after the 5th – 6th year
 - Risk: Overwhelming sepsis (especially if done < 5 years)
 - Precautions: See before

- 5. Other lines of treatment**

- ⊕ Hydroxyurea \rightarrow Induction of Hb F \rightarrow \downarrow Unmatched α chain accumulation \rightarrow \downarrow hemolysis (of limited value due to serious side effects).
 - ⊕ Stem cell transplantation \rightarrow best for patient less than 17 years
 - ⊕ Gene therapy is under research

- 6. Genetic counseling**

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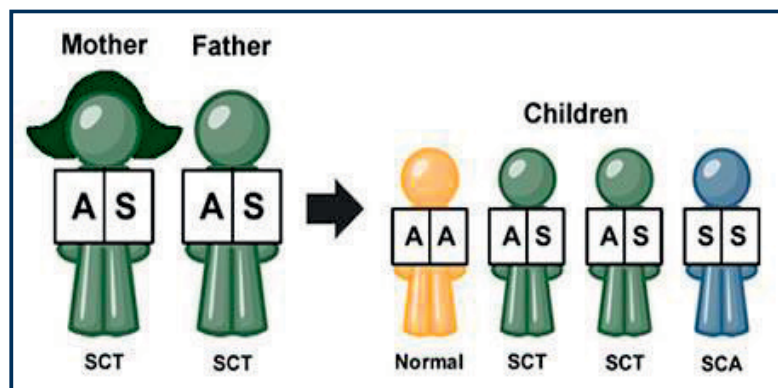
Sickle Cell Disease

Etiology

- Autosomal recessive disorder.
- Due to single amino acid substitution in the number 6 position of the β -chains (valine for glutamic) resulting in new Hb \rightarrow HbS ($\alpha_2\beta_2^{6\text{glut.}} \rightarrow \alpha_2\beta_2^{6\text{val.}} = \text{HbS}$).

Forms

- Sickle cell Anemia; SCA \rightarrow Hb SS ; homozygous
- Sickle cell trait ; SCT \rightarrow Hb AS ; heterozygous



Pathogenesis

HbS can't withstand hypoxia

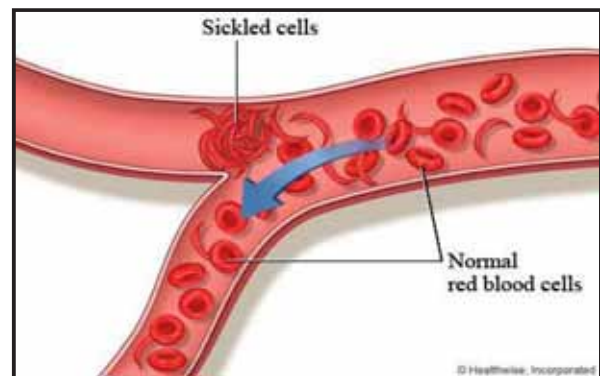
↓
If exposed to low O₂ tensions

↓
HbS polymerize

↓
RBCs distortion

↓
Intra vascular sickling with subsequent

- ↓
1. Aggregation \rightarrow vascular occlusion
 2. Trapping and hemolysis in reticulo endothelial system in the spleen & liver



Clinical picture

- Common in negroes
- Features of anemia
- Features of chronic hemolysis } Starting after the 6th month of age
- Renal disorders \rightarrow proteinuria, nephrotic syndrome, chronic renal failure.

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Crisises

1. Aplastic
2. Hemolytic
3. Megaloblastic
4. Hyperhemolytic (as before)
5. **Vaso occlusive crisis (painful crisis)**

▪ Mechanism

- In vivo sickling → vascular occlusion → ischemia ± infarction.
- Reduced Nitric Oxide bioavailability → vasoconstriction and platelet activation
- WBCs counts are often elevated, adhere to endothelial cells and may further trap sickled red cells, contributing to stasis

▪ Precipitating factors

Fever, Acidosis, Dehydration, Infection & Hypoxia, exposure to cold

▪ Clinically

CNS

- Cerebrovascular stroke
- Retinopathy

Myocardial infarction

Renal infarction

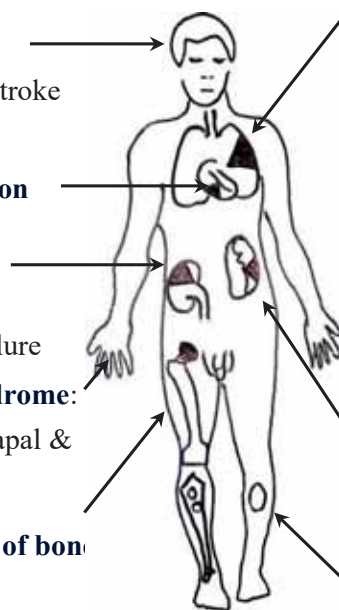
- Hematuria
- Chronic renal failure

Hand and foot syndrome:

Ischemia of metacarpal & metatarsal bones

Avascular necrosis of bone

e.g. femoral head



Acute chest syndrome (ACS):

- Due to pulmonary emboli of necrotic bone marrow (fat emboli) infection or pulmonary infarction
- Clinical Presentation :
 - Gradual or catastrophic.
 - Severe respiratory distress
 - Chest pain, fever
 - Hypoxemia
 - CBC: Leucocytosis
 - CXR: Lung consolidation.

Splenic infarctions → fibrosis → shrinking → autosplenectomy & hyposplenism

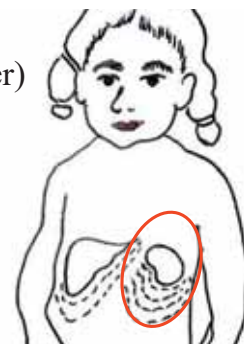
Others e.g. leg ulcers, priapism

6. Splenic sequestration crisis

- Sudden pooling of the blood in the spleen (± the liver)
- Precipitated by dehydration
- Occurs primarily in infants

Clinically

- Acute pallor and acute abdominal pain
- Massive splenomegaly
- Hypovolemic shock.
- Decline in hemoglobin of ≥ 2 g/dL from the patient's baseline hemoglobin; reticulocytosis and a decrease in the platelet count may be present

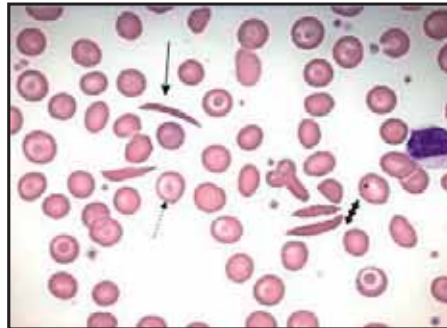


7. Infectious crisis

- Due to hyposplenism (↓opsonization)
- Common organisms: usually encapsulated bacteria
- Site
 - Meningitis (Pneumococci & H. influenza)
 - Pneumonia (Pneumococci)
 - Osteomyelitis (Salmonella)

Investigations

1. For **anemia** → Low Hb% & Ht value.
2. For **chronic hemolysis** → ↓ RBCs survival & ↑ erythropoiesis.
3. For **the cause**
 - a) Blood film:
 - Detect sickle cells in peripheral blood. If not detected, sickling can be enhanced by adding sodium metabisulfite (Sickling test).
 - Howell–Jolly bodies (nuclear remnants) and Sub membranous pits in RBCs may be seen indicating hyposplenism.



- b) Hemoglobin electrophoresis: Show HbSS (90%) & Hb F (2-10%).
- c) Neonatal screening allows early detection , adequate care and longer survival

Treatment

1. **Avoid factors precipitating painful crisis** e.g.
 - Vigorous hydration during exposure to extreme stress
 - Vigorous treatment of infections
2. **Chronic transfusion therapy & iron chelation** (Equivocal)

Indications:

 - Stroke
 - Recurrent painful crisis.
 - Recurrent acute chest syndrome

3. Treatment of crises:

A. Vaso occlusive

- Oxygen
- Hydration ; oral and IV to maintain euvoemia
- Pain control e.g. ibuprofen, acetaminophen, codeine, or morphine
- Empirical antibiotics (cephalosporin and macrolide) for infections
- Simple transfusion target post transfusion hemoglobin ± 10 g/dL
- Exchange transfusion program for recurrent cases

B. Sequestration

- Blood transfusion, typically 5 mL/kg of packed red blood cells
- Exchange transfusion
- Prophylactic splenectomy is the only effective strategy for preventing future life-threatening episodes

C. Aplastic / hemolytic crisis → Blood transfusion

4. Control infection:

- Prophylactic penicillin for life
- Immunize against: Pneumococci & H. influenza

5. Alternative treatment

* Hydroxyurea

Value

- Induction of Hb F (takes time so not suitable for acute therapy)
- Improve RBCs hydration
- The only effective drug proved to reduce the frequency of painful episodes

Dose: typical starting daily dose is 15-20 mg/kg

* Hematopoietic stem cell transplantation.

Sickle cell trait (Hb AS)

- Hemoglobin analysis shows Hb A, typically >50% and (Hb S <50%)
- Asymptomatic but complications do exist e.g.
 - Sudden death during rigorous exercise
 - Splenic infarcts at high altitude
 - Hematuria
 - Bacteriuria
 - Susceptibility to eye injury with formation of a hyphema
 - Susceptibility to renal medullary cancer
- Patients are resistant to lethal effects of falciparum malaria

Auto Immune Hemolytic Anemia (AIHA)

Definition

Hemolytic anemia due to circulating antibodies against patients own RBCs.

Explanation

- Altered immune response (not recognize self-antigens).
- Altered RBCs antigenicity by infection **or** drugs.

Clinical types: According to the type of auto antibodies

Causes	Warm reactive autoantibodies	Cold reactive autoantibodies
Primary Secondary <ul style="list-style-type: none"> ▪ Infection ▪ Vaccination ▪ Disease ▪ Drugs 	<ul style="list-style-type: none"> - 50 % are idiopathic - CMV, HBV - Leukemia/ Lymphoma. - SLE - Methyle Dopa, penicillin, interferon 	<ul style="list-style-type: none"> - Idiopathic - Mycoplasma pneumonia - Infectious mononucleosis - MMR - Lymphoma
Criteria of Antibodies	<ul style="list-style-type: none"> - IgG. - Active at 37°C 	<ul style="list-style-type: none"> - IgM - Active at below 37°C

Clinical picture

1. AIHA due to warm reactive autoantibodies

A. Acute transient type	B. Chronic type
<ul style="list-style-type: none"> - Acute hemolytic anemia with splenomegaly. - In child 2-12 year. - May follow respiratory infection. - Responsive to steroids - Lasting 3-6 months 	<ul style="list-style-type: none"> - Chronic hemolytic anemia. - In child < 2 or > 12 years - May be underlying systemic disease e.g. lymphoma. - Variable response to steroids. - Last months and years

2. AIHA due to cold reactive autoantibodies (*cryopathic hemolytic syndromes*)

A. Cold agglutinin disease

- Cold reacting auto antibodies may present in low titer
- Exposure to triggering agent e.g. Infection with mycoplasma
- Increased auto antibody titer
- Eventual chronic hemolytic anemia



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B. Paroxysmal cold hemoglobinuria

- Due to Donath Landsteiner antibody (IgG which can activate complement)
- Antibodies are biphasic, reacting with red cells in the cold in the peripheral circulation, with lysis occurring due to complement activation when the cells return to the central circulation.
- The lytic reaction is demonstrated in vitro by incubating the patient's red cells & Serum at 4°C and then warming the mixture to 37°C (*Donath-Landsteiner test*)
- Association:
 - Infection with mycoplasma, Ebstein Barr virus, Cytomegalo virus, measles, mumps or chickenpox
 - Congenital or acquired syphilis
- Course: Mild, resolve with infection resolution.

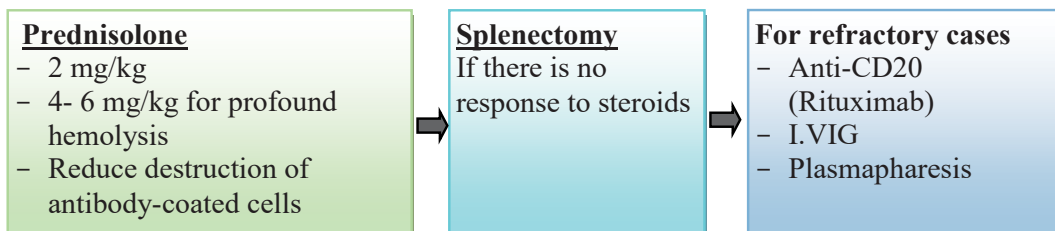
Investigations

- For **anemia** → Low Hb % & ↓ Ht value.
- For **acute hemolysis** (see before)
- For **chronic hemolysis** (see before)
- For **the cause**.
 1. CBC :
 - Micro spherocytes.
 - AIHA plus autoimmune thrombocytopenia → **Evan's Syndrome**.
 2. Positive Coombs test (*Antiglobulin test*)
 - Direct: Detects high titer of autoantibodies coating the RBCs
 - Indirect: Detects the free autoantibodies in patient serum

Treatment

A. AIHA due to warm antibodies

1. Mild and asymptomatic anemia needs only follow up
2. Treatment of symptomatic anemia



B. Cold agglutinin disease

- * Patients should avoid exposure to cold.
- * Steroids and splenectomy are usually ineffective.

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- * Anti-CD20 (Rituximab) has been successful in some cases.
- * Plasmapheresis: for severe cases.

C. Supportive care

- * Treat the underlying cause
- * Blood transfusion:

▪ Value	– Life saving for severe anemia
▪ Problem	– Compatibility testing is complicated by the presence of unspecific red cell autoantibodies
▪ Use	– Small volume of packed RBCs <u>starting</u> with a test dose – Use the least incompatible blood
▪ Disadvantage	– Hard to find totally compatible blood. – Transient effect

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Approach to a Case of Anemia

A. History

1. Onset

- G6PD, spherocytosis can present from neonatal period
- Thalassemia, sickle cell anemia present > 6 month

2. Past history

- Hemorrhage
- Drugs which may induce (aplasia, acute hemolysis in G6PD deficiency).
- Infection or fava beans → G6PD deficiency.



3. Family history → for similar cases and consanguinity for inherited causes.

B. Clinical approach : Search for clinical clues of :

1. Bone marrow failure (Pallor, Purpura, Pyrexia ± organomegaly)



+



+



2. Acute hemolytic anemia



OR



+



Triggers

Acute pallor/jaundice

Dark urine

3. Chronic hemolytic anemia



+



Gradual pallor/jaundice

Organomegaly

Complications

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4. Anemia with congenital anomalies:



Fanconi anemia.

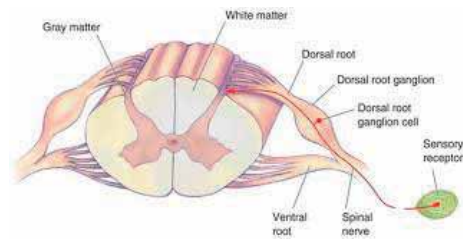


Diamond Blackfan anemia.

5. Anemia with systemic associations



GIT upset (Folic acid deficiency)

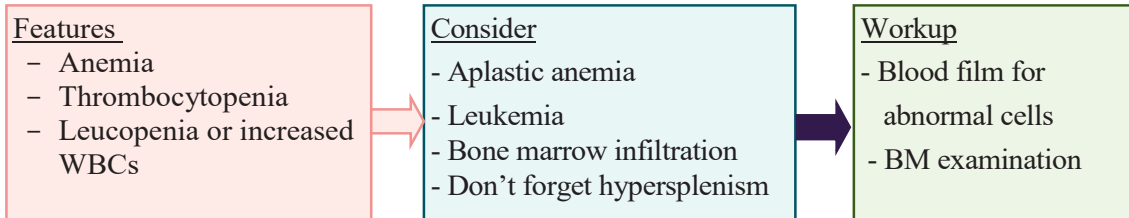


Neuropathy (B₁₂ deficiency)

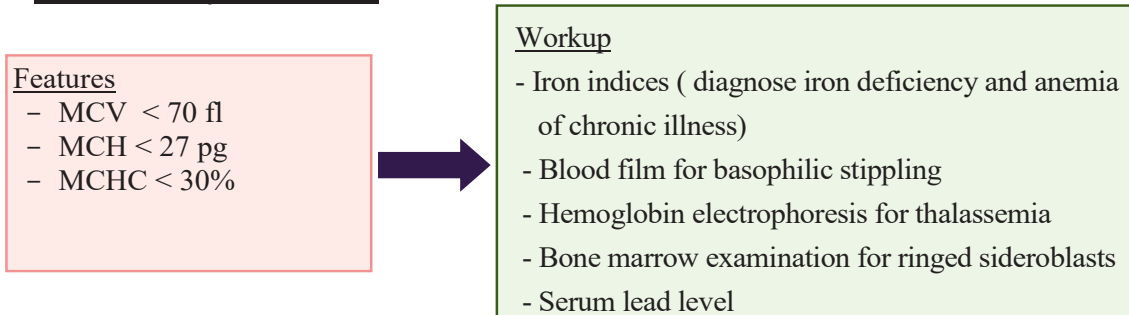
C. Laboratory approach

1. Is it anemia? → ↓ Hb% & ↓ Ht value.

2. Is there bone marrow failure?



3. Is it microcytic anemia?



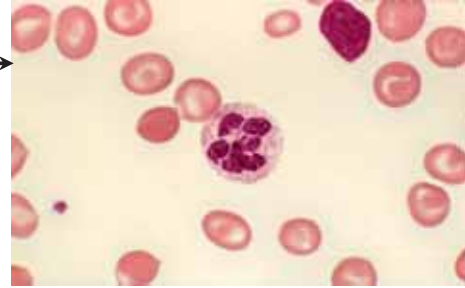
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4. **Is it macrocytic anemia?**

Features : MCV > 85 fl

Causes

- Folic acid and B12 deficiency →
- Other causes:
 - Aplastic or hypoplastic anemia
 - Hepatic disease
 - Hypothyroidism
 - Drugs: antifolate, cytotoxics



Workup: Consider Serum folic acid and B12 assays and Schilling tests

5. **Is it hemolytic anemia?**

- **Is there increased red cell breakdown?**

- Anemia
- ↑Bilirubin: unconjugated, from hem breakdown
- ↑Urinary urobilinogen (no urinary conjugated bilirubin).
- ↑Serum lactic dehydrogenase (LDH), as released from the RBC

- **Is there increased red cell production?**

- Reticulocytosis

- **Is the hemolysis mainly extra- or intravascular?**

- Extravascular hemolysis may lead to splenic hypertrophy and splenomegaly
- Features of intravascular hemolysis are:
 - ↑ Plasma hemoglobin
 - ↓ Haptoglobin & haemopexin(hemoglobin carriers).
 - ↑ Methealbumin
 - ↑ Unconjugated bilirubin, fecal and urinary urobilinogen
 - Hemoglobinuria (and heamosiderinuria)
 - ↑ Serum LDH

Causes : See classification of anemia

Workup:

- Positive Coomb's test: Immune hemolytic anemia
- Negative Coomb's test : Other causes of hemolytic anemia:

Consider

- Osmotic fragility and autohemolysis tests
- Enzyme assays e.g. G6PD deficiency
- Blood film and sickling tests
- Electrophoresis

Hemorrhagic disorders

Hemostasis is the mechanisms of stoppage of bleeding after injury of a blood vessel

I. 1^{ry} Hemostatic Mechanisms

a. Vascular factor

Role

- Reflex vasoconstriction at the site of bleeding.
- Damaged endothelium release serotonin and activate F XII

Assessment

- Bleeding time.
- Hess test

b. Platelets

Criteria

- Life span: 8-10 day
- Count: 150- 400.000 platelets per ml
- Mean platelet diameter: 1- 4 μ M
- Distribution: one third (30%) in the spleen; two-thirds in the bloodstream
- Controlled by thrombopeiotin

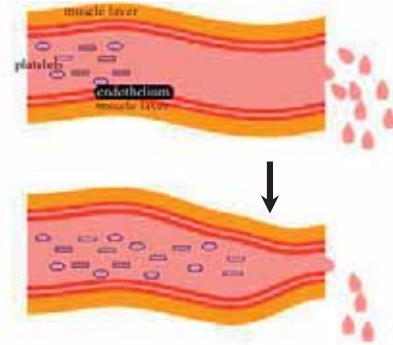
Role

1. Adhesion to exposed collagen fibers (Von Willbrand factor is essential).
2. Aggregation; platelets accumulate at injured site helped by adenosine diphosphate (ADP) & thromboxane $A_2(TXA_2)$
3. Release of:
 - Thromoxane $A_2 \rightarrow \uparrow$ platelet aggregation.
 - Serotonin $\rightarrow \uparrow$ vasoconstriction
 - Platelet factor 3 (PF_3) \rightarrow enhance clotting
 - Thrombasthinine $\rightarrow \uparrow$ clot retraction.

4. Platelet plug formation

Assessment

- Bleeding time \rightarrow normal = 4-8 min.
- Hess test (capillary fragility test) \rightarrow cuff of sphygmomanometer is inflated between systole & diastole for 5 min. \rightarrow if > 5 petechiae appear within 5 cm circle in the forearm \rightarrow +ve test.
- Platelet count ($N = 150 - 400.000 / mm^3$)
- Platelet function tests whenever thromocytopathy is suspected
 - Assess platelet adhesiveness and aggregation.
 - Assay of PF_3 level.
 - Clot retraction test.

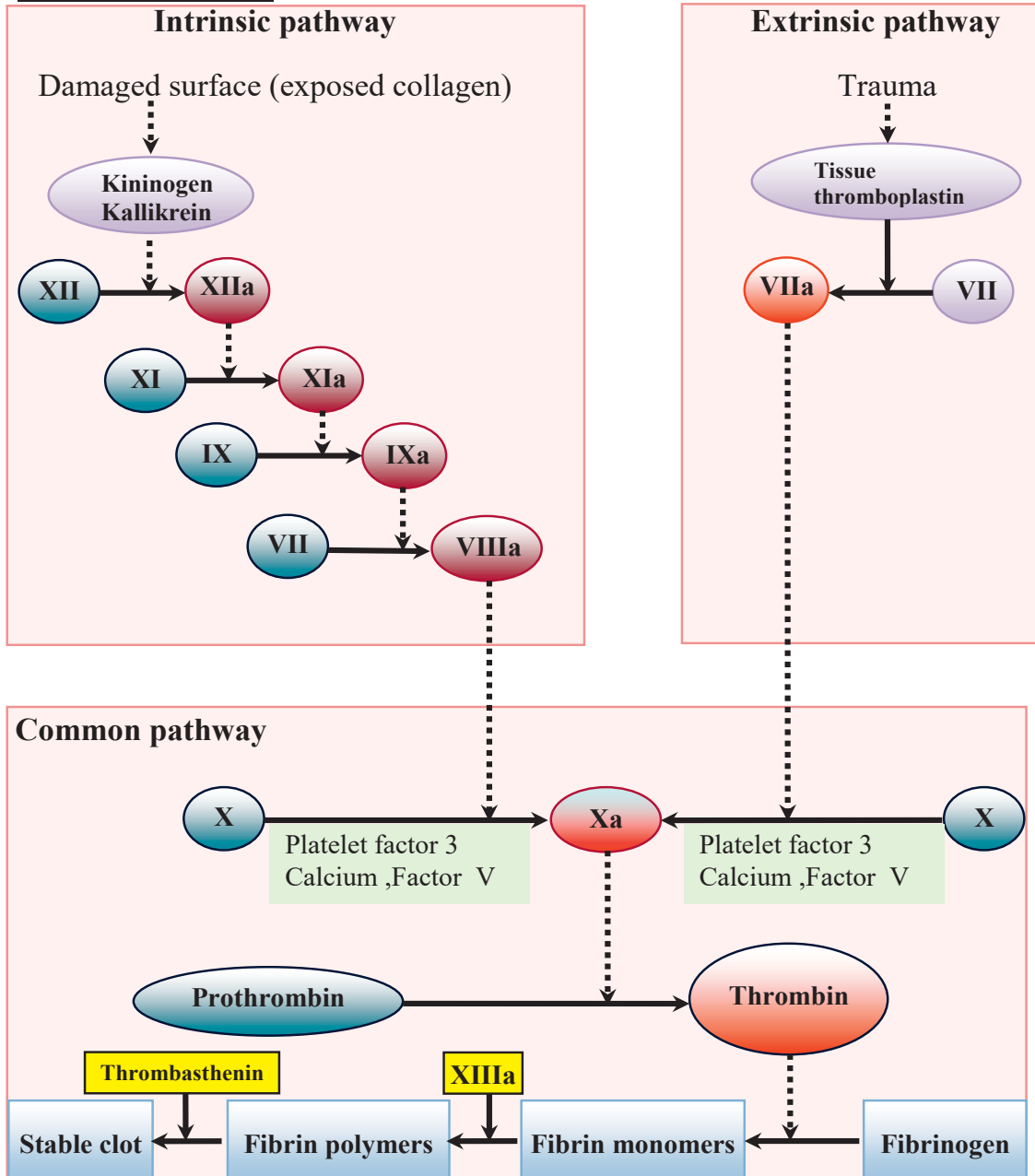


II. Coagulation factors

Criteria

- Most coagulation factors are formed in the liver and circulate in an inactive form (*Pro coagulants*) which are activated in a cascade manner
- Vitamin K dependent factors → II, VII, IX, X.
- Most activation reactions occurred on the surface of the platelets
- Calcium is a cofactor for many steps of activation cascade ;particularly the common pathway

Activation cascade



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Coagulation factors names

I	Fibrinogen	II	Prothrombin
III	Tissue thromboplastin	IV	Calcium
V	Labile factor	VII	Stable factor
VIII	Anti-hemophilic factor	IX	Christmas factor
X	Stuart Prower factor	XI	Plasma thromboplastin antecedent
XII	Hageman factor	XIII	Fibrin stabilizing factor

Others : High Molecular Weight Kinonogen , Kallekrein

Assessment:

- 1. Clotting time** → normal = 8-12 **min.**
rough test → prolonged with defects in any phase
- 2. Thrombin time (TT)** → normal = 15-20 Sec.
 - Time needed to plasma to clot after addition of bovine thrombin
 - Prolonged in fibrinogen deficiency.
- 3. Prothrombin time (PT)** → normal = 12-14 Sec.
 - Time needed to plasma to clot after addition of thromboplastin & Calcium.
 - Test extrinsic & common pathways.
- 4. Partial thromboplastin time (aPTT)** → normal = 25-40 Sec.
 - Time needed for plasma to clot after addition of kaolin, Calcium & platelets.
 - Test intrinsic & common pathways.

Interpretation

Defect in	PT	PTT	Specific
Common pathway (X,V,II,I)	Prolonged	Prolonged	Specific factor assay
Extrinsic pathway (VII)	Prolonged	Normal	
Intrinsic pathway (XII,XI,IX,VIII)	Normal	Prolonged	

N.B: Prolonged both PT & PTT also occur in multiple factors deficiency e.g.

- Liver cell failure
- Vitamin K deficiency
- Disseminated Intra vascular Coagulation (DIC)

5. Specific tests e.g. Von Willbrand disease:

- Prolonged both bleeding time and clotting time
- Decreased both F VIIIc & F VIIIa
- Von Willbrand factor assay

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Control of coagulation factors

1. Natural coagulation inhibitors

Value: localizes thrombosis to the site of injury.

a. Antithrombin (AT)

- Potent inhibitor of factors XIa, IXa, Xa, and thrombin.
- Its action is greatly potentiated by heparin.

b. Activated protein C

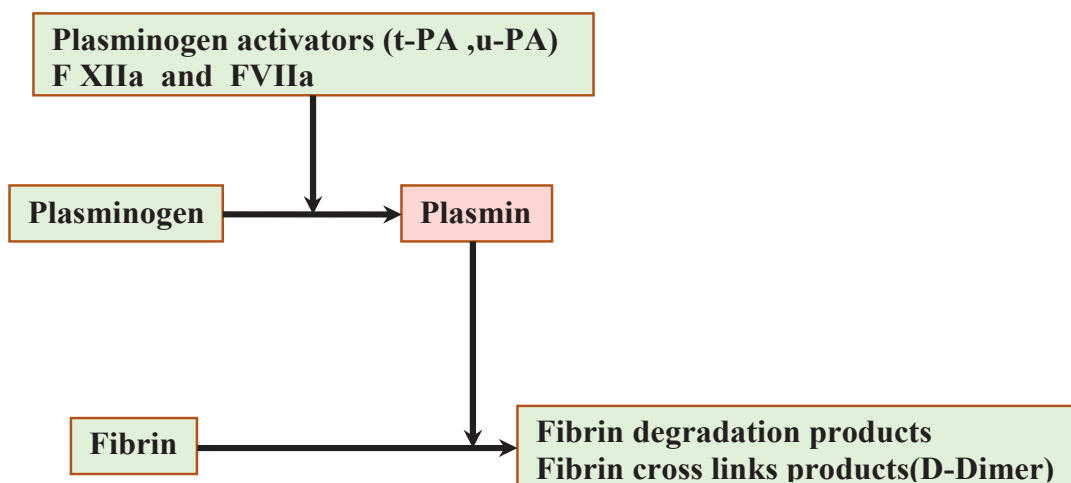
- Vitamin K dependent protein
- Activated by thrombin
- Activated protein C inactivates factor V and factor VIII

c. Protein S

- This is a cofactor for protein C

2. Fibrinolytic system: (Fibrinolysis)

- Plasmin is generated from its inactive precursor plasminogen
- This is achieved principally via tissue plasminogen activator (t-PA) released from endothelial cells.
- Some plasminogen activation may also be promoted by urokinase, produced in the kidneys (u-PA).
- Plasmin breaks down fibrinogen and fibrin into fragments X, Y, D and E, collectively known as fibrin (and fibrinogen) degradation products (FDPs).
- D-dimer is produced when cross-linked fibrin is degraded.
- Fibrinolysis helps to restore vessel patency after vascular damage.



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Purpura

Definition: Group of disorders characterized by:

- 1- Multiple, spontaneous hemorrhages in the skin and mucous membranes.
- 2- Range from pin point (petechiae) to several centimeters (ecchymosis)
- 3- Petechiae are purple in color, not elevated, do not blanch on pressure, not pruritic

Possible bleeding sites:

- Skin: petechiae, ecchymosis
- Mucous membranes: oral, gingival, conjunctiva,..
- Orificial: epistaxis, hemoptysis, hematuria, melena..
- Internal: intracranial, retinal, pleural, pericardial,..

Causes

I. Non thrombocytopenic purpura: (Normal platelet count)

1. Vascular purpura

a. Hereditary: e.g.

Ehler Danlos Syndrome

- Defect in type III collagen in connective tissue.
- Clinical picture
 - Hypermobile joints
 - Purpura



b. Acquired

Vasculitis

- Henoch schonlein purpura
- Sepsis (meningeococcal).
- Infective endocarditis

Weak blood vessels

- Scurvy → defective connective tissue collagen.
- Cushing syndrome

2. Thrombasthenia (Platelet dysfunction; Thrombocytopathy)

a. Hereditary thrombocytopathy

- Defective adhesion: Von Willbrand disease , Bernard Soulier disease
- Defective aggregation: Glanzmann disease.

b. Acquired

- Uremia (Renal failure)
- Cholemia (Liver failure)
- Drug induced: Aspirin (↓ ADP & Thromboxan A2), Heparin
- Autoimmune: SLE

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II. Thrombocytopenic purpura

Defined as platelet count $<100.000/\text{mm}^3$

A. Decreased production

With decreased marrow megakaryocytes

I. Congenital

1. **Fanconi anemia**

2. **Thrombocytopenia absent radii (TAR) syndrome**

- Thrombocytopenia
- Absent or hypoplastic radii
- Other associated anomalies e.g. congenital heart disease



3. **Wiskott – Aldrich syndrome**

- Sex linked recessive disorder
- Microthrombocytopenia
- Infantile eczema and bloody diarrhea are the commonest presentation
- Combined immunodeficiency



Petechiae due to thrombocytopenia



Eczema



Pneumonia and other infections

II. Acquired

1. Aplastic anemia
2. Bone marrow infiltration (e.g. Leukemia).
3. Advanced megaloblastic anemia

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B. Increased destruction

With compensatory increased marrow megakaryocytes

I. Immunologic

- Primary : Idiopathic thrombocytopenic purpura
- Secondary to
 - Immunologic diseases e.g. SLE
 - Post transfusion purpura
 - Drug induced e.g. Heparin, Phenyton
 - Malignancy e.g. Lymphoma

II. Non immunologic

- Microangiopathic hemolytic anemia e.g. DIC, hemolytic uremic syndrome.
- Hypersplenism.
- Acute infections, Sepsis.
- Thrombotic thrombocytopenic purpura
- **Kasabach-Merritt syndrome (KMS):**



- Combination of giant cavernous hemangioma, thrombocytopenia, and coagulopathy
- Platelets are trapped and destroyed in the giant cavernous hemangioma
- Frequently associated with disseminated intra vascular coagulation
- Treatment : steroids ,interferon, surgical ligation of feeding vessels

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Idiopathic Thrombocytopenic Purpura (ITP)

(Immune Thrombocytopenic Purpura)

Definition: Purpura characterized by:

- Shortened platelets survival due to antiplatelet antibodies
- Thrombocytopenia ($< 100.000 /\text{mm}^3$).
- Increased bone marrow megakaryocytes.
- Absent other identifiable thrombocytopenic disorders (a diagnosis of exclusion).

Pathophysiology

- Anti-platelets antibodies triggered by preceding viral infection
- Antibodies coated platelets is trapped in the spleen by macrophage Fc receptors
- Spleen is the primary site for antibody production and platelets destruction.

Clinical picture

Incidence

- Age: peak between 1 – 4 years
- Sex incidence: Equal

Acute purpura

- The classic presentation of ITP is a previously healthy 1-4 yr old child who has sudden onset of generalized petechiae and purpura.
- The parents often state that the child was fine yesterday and now is covered with bruises and purple dots.
- Often there is bleeding from the gums and mucous membranes, particularly with profound thrombocytopenia (platelet count $< 10 \times 10^9/\text{L}$).
- There is a history of a preceding viral infection 1-4 wk before the onset of thrombocytopenia in 50-60% of patients.



Important exclusions

1. No significant organomegaly ;however tip of the spleen is palpable in 10 % of cases
2. No significant pallor except with severe bleeding or associated autoimmune hemolytic anemia (Evans syndrome)

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Clinical classification of bleeding severity

1	No symptoms
2	Mild symptoms: <ul style="list-style-type: none"> – Bruising and petechiae – Occasional minor epistaxis – Very little interference with daily living
3	Moderate: <ul style="list-style-type: none"> – More severe skin and mucosal lesions – More troublesome epistaxis and menorrhagia
4	Severe: <ul style="list-style-type: none"> – Bleeding episodes: menorrhagia, epistaxis, melena—requiring transfusion or hospitalization – Symptoms interfering seriously with the quality of life

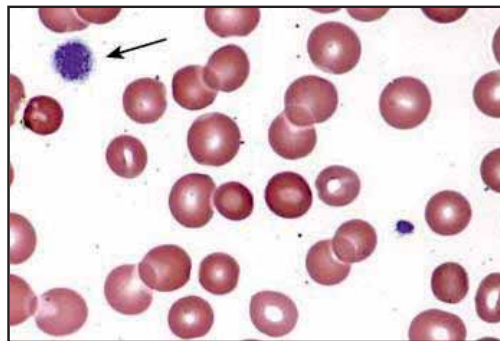
(Nelson textbook of pediatrics, 2016)

Diagnosis

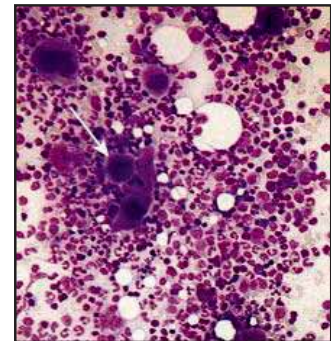
- Isolated thrombocytopenia in healthy child with normal blood smear
- **Blood smear:**
 - Platelet count → always $< 100,000 / \text{mm}^3$; platelets usually large sized
 - Normal WBCs and RBCs (except in Evans and severe bleeds); no abnormal cells
- **Bone marrow examination**
 - Increased numbers of megakaryocytes, many of which appear immature
 - Normal myeloid and erythroid cells

Indications for bone marrow examination include

1. Abnormal WBC count or differential
2. Unexplained anemia
3. History and physical examination suggestive of a bone marrow failure syndrome or malignancy.
4. No response to supportive therapy and steroid therapy needs to be started



Blood smear

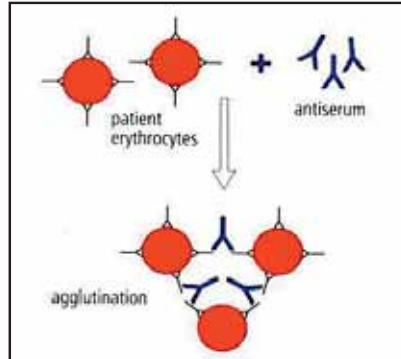


Bone marrow smear

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Other tests

- A direct Coombs should be done if there is unexplained anemia to rule out Evans syndrome or before instituting therapy with IV anti-D.



- In adolescents, an antinuclear antibody test should be done to evaluate for SLE.
- HIV studies should be done in at-risk populations, especially sexually active teens.
- Platelet antibody testing is seldom useful in acute ITP.

Prognosis

- Spontaneous resolution occurs in **80 %** of children with acute ITP within 6 mo.
- About **20%** of children with acute ITP go on to have chronic ITP.
- Fewer than **1%** of patients develop an intracranial hemorrhage
- Therapy does not appear to affect the natural history of the illness. There is no evidence that therapy prevents serious bleeding.
- The prognosis may be related more to age, as ITP in younger children is more likely to resolve whereas the development of chronic ITP in adolescents approaches 50%.

Differential Diagnosis

From other causes of **purpura** :

	ITP	BM aplasia	BM infiltration	Hypersplenism
Clinical	- Isolated purpura in clinically well child	- Purpura - Pallor - Pyrexia - No organomegaly	- Purpura - Pallor - Pyrexia - Organomegaly	- Purpura - Pallor - Pyrexia - Splenomegaly
Blood film	- ↓Platelets	- Pancytopenia	- Pancytopenia	- Pancytopenia
Bone Marrow	- Megakaryocyte hyperplasia	- Hypoplastic	- Infiltrated	- Hyperplastic

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Treatment of ITP

I. No therapy (Observation)

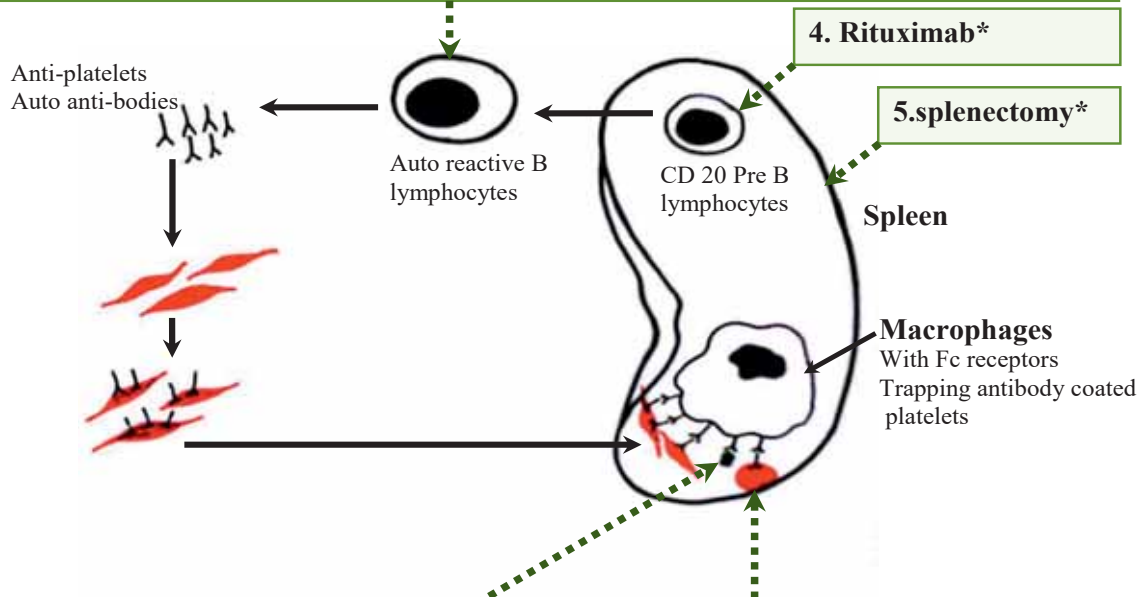
- For patients with minimal, mild, and moderate symptoms
- Education and counseling of the family about benign nature of ITP
- Avoid trauma, aspirin, contact sports.

II. Drug therapy

- Indicated for significant bleeding with platelet counts below $20 \times 10^9/L$
- Aim : to raise platelets above theoretically safe level $>20 \times 10^9/L$

1. Prednisone

- Decrease platelet antibodies production and phagocytosis of antibody coated platelets
- Standard dose: 2 mg /kg/day for 21 days → gradually tapered
- High dose :4 mg / kg/day for 4 days → less steroid side effects
- Two thirds will respond but relapse is common
 - Standard dose : response in 1 week
 - High dose : platelets $> 20 \times 10^9/L$ in 2 days , platelets $> 50 \times 10^9/L$ in 3-4 days



2. Intravenous Immunoglobulin (IVIG)

- Block macrophage Fc receptors → protect platelets from destruction
- Dose : **0.8-1** gm/kg for 1- 2 days
- Induces a *rapid rise* in platelet count (usually $>20 \times 10^9/L$) in 95% of patients within 2 days
- Very useful in serious bleeding or urgent surgery

3. intravenous anti D (Win Rho)

- Coat Rh positive RBCs → RBC-antibody complexes bind to macrophage Fc receptors → platelet escape destruction with transient mild hemolysis (Patient must be unsplenctomized, Rh positive , with Hb > 9 gm/dl)
- Should not be used with IVIG
- Dose : **50-75** $\mu g/kg$
- Causes a rise in platelet count to $>20 \times 10^9/L$ in 85% of patients within 48-72 hr

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* Splenectomy

- Indications
- Severe ITP with life threatening bleeding unresponsive to steroids and intravenous immunoglobulin
 - A second line therapy for Chronic ITP uncontrolled medically
- Response
- Two-thirds will achieve a normal platelet count

* Rituximab

- Nature Anti CD20 monoclonal antibody
- Role Deplete auto reactive B cells (mainly for chronic ITP)

Treatment of life threatening bleeding (e.g. intracranial hemorrhage):

1. Resuscitation (including blood transfusion if needed)
2. Platelet transfusion (especially if platelets count $< 20.000/\text{mm}^3$).
 - * Have shorter life span but can be life saving in life threatening hemorrhage or in case of emergency operation e.g. splenectomy
 - * Dose: 0.2 platelet units per kg as a bolus followed by continuous infusion if required
3. I.V. immunoglobulin 1gm/kg/day for 2-3 days.
4. I.V. methylprednisolone 30 mg / kg/day for three days
5. Emergency splenectomy (not usually recommended).
6. Recombinant human factor VIIa (Rhu VIIa)

Take home messages

- There are no data showing that treatment affects either short- or long-term clinical outcome of ITP
 - Platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present
- (Nelson Textbook Of Pediatrics, 2016)



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Anaphylactoid Purpura (Henoch Schonlein Purpura)

Definition

- The commonest vasculitis of childhood
- Characterized by immunoglobulin (Ig) A deposition in the small vessels mainly in the skin, joints, gastrointestinal tract, and kidney.
- Peak age incidence between 2-8 years ; more in males
- May follow drugs or upper respiratory viral or bacterial (sterptococi) infection

Clinical picture

1. Skin rash

- In 100 % of cases
- Skin lesions are usually symmetric and occur in gravity-dependent areas (lower extremities) or on pressure points (buttocks and extensor surfaces)
- Start as palpable erythematous maculopapular rash then become purpuric (petechiae).
- May be pruritic.
- Association: Non pitting angioedema of hands, feet, lips, scalp



Typical HSP rash



Angio edema of dorsa of hands

2. Arthritis/arthralgia

- In 75 % of cases.
- Oligoarticular usually in large joints e.g. ankle & knee.
- Swollen, hot, tender, with limitation of movement.
- Usually resolves within 2 wk but can recur without residuals



Swollen ankles with typical HSP rash, and angio edema of dorsa of feet

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3. Gastro intestinal tract manifestations

- In 80% of cases
- Presentations
 - Vomiting, diarrhea, paralytic ileus
 - Bowel angina (postprandial abdominal pain, bloody diarrhea)
- Complications
 - Intussusception (? due to submucosal hematoma)
 - Bowel infarction and perforation



4. Renal

<u>Mainly</u>	<u>Rarely</u>
- Hematuria	- Proteinuria
- Acute nephritis	- Nephrotic syndrome.
- Normal renal function	- Chronic renal disease develops in 1-2% of children with HSP, and approximately 8% of those with HSP nephritis go on to have end-stage renal disease.

5. Others vasculitic manifestations

- Neurological → seizures, paresis.
- Testis → Hemorrhage.

Diagnosis

- The diagnosis of HSP is a clinical one
- No laboratory finding is diagnostic of HSP

1. For purpura :

- Normal platelet count & function (may be thrombocytosis) .
- Normal coagulation profile.

2. For renal manifestations

- Urine analysis for → RBCs, RBCs casts, proteinuria
- Renal function tests
- Renal biopsy for renal insufficiency or heavy proteinuria

3. For gastro intestinal manifestations

- Stool analysis for gross or occult blood
- Abdominal ultrasound and/or abdominal CT for intussusception

4. Others

- Increased ESR and serum IgA
- Biopsies of skin and kidney
 - Can give diagnostic clue, particularly in atypical or severe cases
 - Shows characteristic leukocytoclastic vasculitis with intramural granulocytes in small arterioles and/or venules with deposits of IgA

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Treatment

1. Symptomatic and supportive care e.g. bed rest for joint pain

2. Medications :

- Anti-inflammatory medicines e.g. ibuprofen or painkillers e.g. paracetamol may help relieve some of the joint pain
- Empiric use of prednisone (1 mg/kg/day for 1 to 2 wk, followed by taper)
- Evidence exist to support use of steroids for bowel angina(Reduces abdominal pain) and neurological manifestations
- It does not alter overall prognosis nor prevent renal disease

3. Follow up

It is recommended that children with HSP undergo serial monitoring of blood pressure and urinalyses for 6 mo after diagnosis, especially those who presented with hypertension or urinary abnormalities.

Coagulation Disorders

A. Hereditary

1. Intrinsic pathway disorders:

- Factor VIII deficiency (Hemophilia A)
- Factor IX deficiency (Hemophilia B or Christmas disease).
- Factor XI deficiency (Hemophilia C).
- Factor XII deficiency
- Von Willbrand disease (Vascular hemophilia) \Rightarrow commonest disorder.

2. Extrinsic pathway disorders

- Factor VII deficiency

3. Common pathway disorders:

- Factors II, X deficiency
- Factors V (Para Hemophilia)
 - Fibrinogen deficiency:
 - Congenital afibrinogenaemia.
 - Congenital dysfibrinogenaemia
- Factor XIII deficiency

B. Acquired

- 1- Vitamin K deficiency
 - * Hemorrhagic disease of newborn: see neonatology
 - * Vitamin k malabsorption due to:
 - Biliary atresia / obstruction
 - Fat malabsorption e.g. celiac disease,
 - * Vitamin K antagonists
- 2- Liver cell failure
- 3- Disseminated intravascular coagulation (DIC).
- 4- Others:
 - Massive transfusion syndrome
 - Medications: heparin , thrombolytics , L-Asparaginase
 - Inhibitors of coagulation due to:
 - a. Hemphelia inhibitors
 - b. Auto immunes diseases : SLE , rheumatoid arthritis

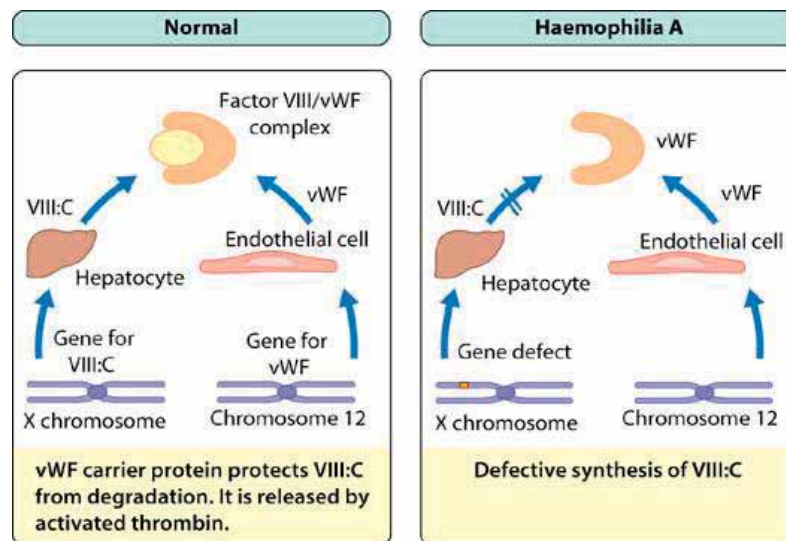
Hemophilia A (classic hemophilia)

Definition

- Sex-linked recessive coagulation defect due to deficiency of factor VIII-C
- 20% of cases are new mutations.
- Hemophilia A represents 80% of all hemophiliacs

Pathophysiology

- Factor VIII-C is synthesized by the liver and reticuloendothelial system
- In plasma, factor VIII-C is stabilized and protected from degradation by Von Willebrand factor(vWF) protein
- In the presence of normal vWF, the half-life of factor VIII-C is approximately 12 hours, whereas in the absence of vWF, the half-life of factor VIII-C is reduced to 2 hours



(Illustrated paediatrics ,Tom Lissauer)

Pattern of deficiency

- Hemostatic level of F VIII-C is >30- 40U/L (30-40%); below which bleeding occur
- Plasma level of Factor VIII-C in carrier females is between **30-50 %**

Clinical picture

Severity of bleeding episode is dependent on the plasma level of factor VIII-C and the severity of trauma

	Severe disease	Moderate disease	Mild disease
F VIII-C	< 1%	1-5%	5-25%
Bleeding trigger	Bleed spontaneously	Bleed with minor trauma	Bleed with severe trauma

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1. In neonate

Unusual bleeding from the
circumcision site or umbilical stump

**2. External bleeding**

e.g.

- Epistaxis
- Dental /mouth bleeding
- GIT bleeding
- Hematuria

**3. Skin bleeding**

- Easy bruising
- Ecchymotic patches
- Hematomas
- No petechiae

**4. Hemarthrosis**

- The hallmark of hemophilia A and B
- Affects mainly the big joints of the lower limbs
- Affected joint become swollen, red, hot, and tender with limited mobility
- Tend to be recurrent
- Recurrent hemarthrosis → joint fibrosis / ankylosis & muscle atrophy

**5. Internal bleeding**

e.g.

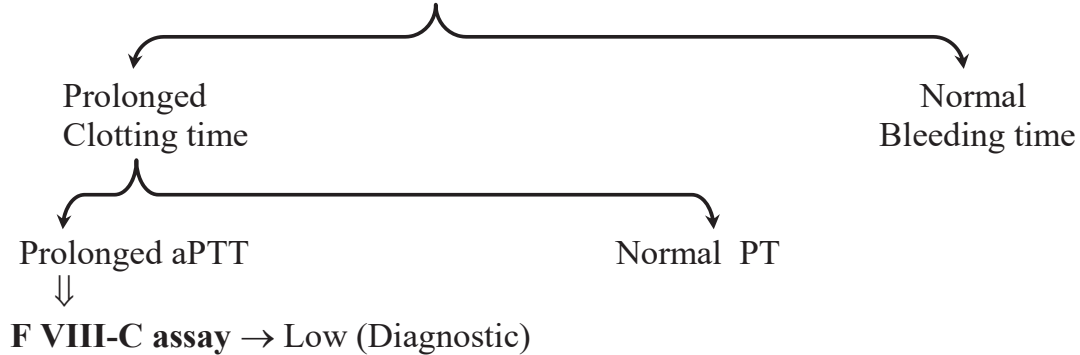
- Muscle hematoma
- Intracranial
- Retroperitoneal
- Hemothorax



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Investigations

1. For diagnosis



2. For carrier detection

- Direct F VIII-C gene mutation analysis.

3. For prenatal diagnosis

- Chorionic villous sample or amniocentesis and gene mutation analysis.
- Fetal blood sampling → immunoradiometric assay of F VIII-C antigen

Treatment

1. Primary prophylaxis

- Regular F VIII replacement 20 unit/kg 3 times a week
- The National Hemophilia Foundation recommends prophylaxis for children with severe hemophilia to reduce frequency of bleeding episodes. Usually, such programs are initiated with the first joint hemorrhage.
- Hepatitis B and A vaccination.
- Avoid trauma, I.M. injections & aspirin.



2. During bleeding episodes/peri operative

a. Factor VIII replacement

1. IV infusion recombinant factor VIII ⇒ dose is according to site & severity
 - Minor bleeding: the factor VIII level should be raised to 20–30 IU/dL.
 - Severe bleeding: the factor VIII should be raised to at least 50 IU/dL.
 - Major surgery: the factor VIII should be raised to 100 IU/dL preoperatively and maintained above 50 IU/dL until healing occurred.
2. Others e.g.
 - Cryoprecipitate
 - Fresh frozen plasma



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b. Ancillary therapy**a. Desmopressin**

(D - amino- D - Arginine VasoPressin; DDAVP)

- Role: Increases F VIII level by 4 folds
- Alternative to recombinant F VIII in mild bleeding in mild hemophilia
- Intra nasal or Intravenous (0.3 µ gm /kg in 50 ml saline over 20 min)

**b. Antifibrinolytics**

- Role: inhibit fibrinolysis → stabilizes the clot
- Indication: - Adjuvant therapy to recombinant factor VIII in mucosal bleeding (oral bleeding, or epistaxis) due to high fibrinolysins in saliva
- Avoided: - In urinary tract hemorrhages to avoid risk of intra renal clot formation and obstructive uropathy
- Examples: Epsilon Amino Caproic Acid (EACA), Tranexamic acid

c. Special situations e.g.

	F VIII dose (IU/kg)	Other lines
Intra cranial hemorrhage	50 IU/kg / 8 hours Then / 12 hours for 8 days Then / 24 hours for 7 days	Urgent hospitalization
Epistaxis and oral bleeding	25 IU/kg / day	EACA 50 mg/kg/6hrs For 1 week
Hematuria and Hemarthrosis*	25- 50 IU/kg / 12 hours for 1-3 days	Followed by prednisone short course for 3-5 days

*Hemarthrosis care include rest, immobilization, cold compresses and elevation

Complications of hemophilia**A. Due to bleeding**

- Hemophilic arthropathy→joint stiffness & Muscle atrophy
- Severe intracranial hemorrhage.
- Severe blood loss→ hypovolemic shock

B. Complications of transfusion (See chronic transfusion in thalassemia)**C. Complications of factor VIII therapy**

1. Hypersensitivity reactions
2. Factor VIII inhibitors (Antibodies)
 - Develop in about 5-10 %
 - Hemorrhage become refractory to treatment
 - Inhibitors (measured by Bethesda Units) should be screened for annually

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■ Treatment options

Low responders (< 5 Bethesda Units)	High dose factor VIII
High responders (>10 Bethesda Units)	<ol style="list-style-type: none"> 1. Prothrombin complex concentrate (contain prothrombin, F VII, F IX, F X) 2. Recombinant activated factor VII (<i>NovoSeven</i>) 3. Immune tolerance induction: daily infusion of the missing protein till inhibitors disappears 4. Rituximab (Anti CD -20)

Other hemophilias

Hemophilia B (Christmas disease)

- Factor IX deficiency.
- Incidence: 1 / 50.000 (in contrast to hemophilia A which is 1 / 10.000)
- Sex-linked recessive disorder.
- As hemophilia A **but** milder.
- Treated by: Recombinant factor IX or factor IX concentrate given/24 hours.
- Prophylactic treatment: Recombinant factor IX twice a week.

Hemophilia C

- Factor XI deficiency.
- Autosomal recessive disorder so can affect both sexes.
- Very mild disease.
- Treated by fresh frozen plasma given / 48 hours.

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Von Willebrand Disease; VWD (Vascular Hemophilia)

- Von Willebrand factor (VWF) is a large multimeric glycoprotein
- Synthesized in megakaryocytes and endothelial cells
- Stored in platelet and endothelial cell

Functions : VWF is essential for

- Platelet adhesion to sub endothelial matrix after vascular damage
- Carrier for F VIII protecting it from proteolysis

Deficiency

- o **VWF** deficiency results in: Platelet dysfunction and decrease plasma F VIII.
- o Pattern of deficiency: low (type 1) **or** abnormal (type 2) **or** absent (type 3).
- o Inherited mainly as autosomal dominant disorder
- o Diagnosed more in women than in men
- o The commonest hereditary bleeding disorder , and some reports suggest that it is present in 1-2% of the general population

Clinical picture

- Mild bleeding: commonly mucocutaneous hemorrhage including skin bruising, epistaxis, gum bleeding and menorrhagia.
- May be post operative bleeding
- Very rarely severe bleeding episodes or hemarthrosis (type 3)

Because VWF is an acute-phase protein, stress will increase its level. Thus, patients may not bleed with procedures that incur major stress, such as appendectomy and childbirth, but may bleed excessively at the time of cosmetic or mucosal surgery (Nelson Textbook Of Pediatrics, 2016)

Investigations

A. Screening

- Long bleeding time + long PTT + Normal PT
- Normal results on screening tests do not preclude the diagnosis of VWD

B. Diagnostic

Note: if the history is suggestive of a mucocutaneous bleeding disorder, VWD testing should be undertaken

Tests

1. Quantitative assay for VWF antigen
2. Testing for VWF activity (Ristocetin cofactor activity)
3. Determination of VWF structure (VWF multimers)
4. F VIII assay (F VIII decreases in some subtypes ;Type 2N vWD)
5. Platelet count And platelet adhesion test

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Treatment

1. Minor bleeds require no treatment
2. Desmopressin is effective especially in type 1 (mainstay of treatment)
3. Antifibrinolytics (e.g. EACA) → as adjuvant treatment in oral bleeding.
4. VWF replacement therapy

Indications

- For severe bleeding episodes.
- The only effective treatment in type 3.

Use

- Cryoprecipitate
- Fresh frozen plasma.
- Purified or recombinant VWF concentrates (containing no factor VIII) may become available in the near future

Disseminated Intravascular Coagulation (DIC)

Wide spread activation of clotting factors all over the body resulting in:

- Thrombosis and ischemia of different vessels.
- Consumption of coagulation factors → bleeding.
- Microangiopathic hemolytic anemia & thrombocytopenia.

Predisposing factors

- Severe tissue damage e.g. in shock, dehydration, burn, hyperthermia, crush injury, asphyxia.
- Sepsis: meningococcal, pneumococcal, rickettsia, malaria, viral
- Snake bites
- Tumors e.g. AML, disseminated malignancy e.g. neuroblastoma
- Incompatible blood Transfusion
- Protein C deficiency; congenital or acquired with purpura fulminans
- Gastro intestinal causes e.g. fulminant hepatitis, pancreatitis, severe inflammatory bowel disease

Clinical picture

- **Manifestations of the cause.**
- Bleeding first occurs from sites of venipuncture, ecchymosis, purpura.
- Thrombotic manifestations: gangrene in the skin, subcutaneous tissues, extremities or renal infarction.
- Severe anemia → Shock
- May be multi organ system failure

Investigations(3C)

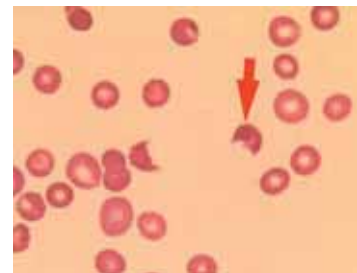
1. Investigations for the Cause

2. Coagulation profile:

- Defective all phases of coagulation ; prolonged PT, aPTT, thrombin time, and low fibrinogen.
- Prolonged bleeding time
- Fibrinogen degradation products (FDPs, D-dimers) appear in the blood. The D-dimer assay is as sensitive as the FDP test and more specific for activation of coagulation and fibrinolysis.

3. CBC/blood smear:

- Anemia
- Fragmented and burr- and helmet-shaped red blood cells (schistocytes)
- Thrombocytopenia



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Treatment

The 1st 2 steps in the treatment of DIC are the most critical:

1. Aggressive treatment the trigger that caused DIC and
2. Restore normal homeostasis by correcting the shock (fluids/blood transfusion), acidosis, and hypoxia that usually complicate DIC.
3. Control of bleeding
 - Platelet infusions for marked thrombocytopenia .
 - Cryoprecipitate for hypofibrinogenemia.
 - Fresh frozen plasma for replacement of other coagulation factors and natural inhibitors.



4. Heparin use is controversial ; used only in:
 - Purpura fulminans
 - Chronic low grade DIC with giant hemangioma
 - Severe ischemic manifestations.

Prognosis

Generally bad , primarily dependent on the outcome of the treatment of the primary disease and prevention of end-organ damage

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Evaluation of a bleeding child

Is there an emergency?

- * Does the patient need immediate resuscitation or senior help?
- * Is the patient about to exsanguinate (shock, coma)?
- * Is there hypovolemia (postural hypotension, oliguria)?
- * Is there CNS bleeding (meningism, CNS, and retinal signs)?
- * Is there an underlying condition that escalates this apparently minor bleeding into an evolving catastrophe e.g .
 - GIT bleeding in a jaundiced child (ie, coagulation factors already depleted)
 - Bleeding in someone who is already anemic

History

Present history

- Age of onset: early in hereditary coagulaopathy hemophilia
- Site of bleeding: skin, mucosal or internal
- Duration of bleeding
- Outcome of bleeding
- Relation to trauma or viral respiratory infection
- Secondary cause eg drugs (warfarin), alcohol, liver disease, sepsis
- Severity of bleeding: is it spontaneous or traumatic

Past history: Drugs/ operations / transfusions

Family history: For similar cases or consanguinity

Menstrual history: For adolescent girls

Examination

* Purpura

- Multiple, spontaneous hemorrhages in the skin & mucous membranes.
- Range from pin point (petechiae) to several centimeters (ecchymosis)

* Coagulopathy

- Hematomas in deep structures e.g. muscle hematomas
- Extensive ecchymosis
- Hemarthrosis

⊕ Associations

- Organ system failures
- Other systems involvement
- Underlying systemic disease

Workup

1. Complete blood count / blood film
2. For purpura (See before)
3. For coagulopathy: (See before)
4. For an etiology /association e.g. sepsis workup in DIC, renal function in HUS,....

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Leukemia

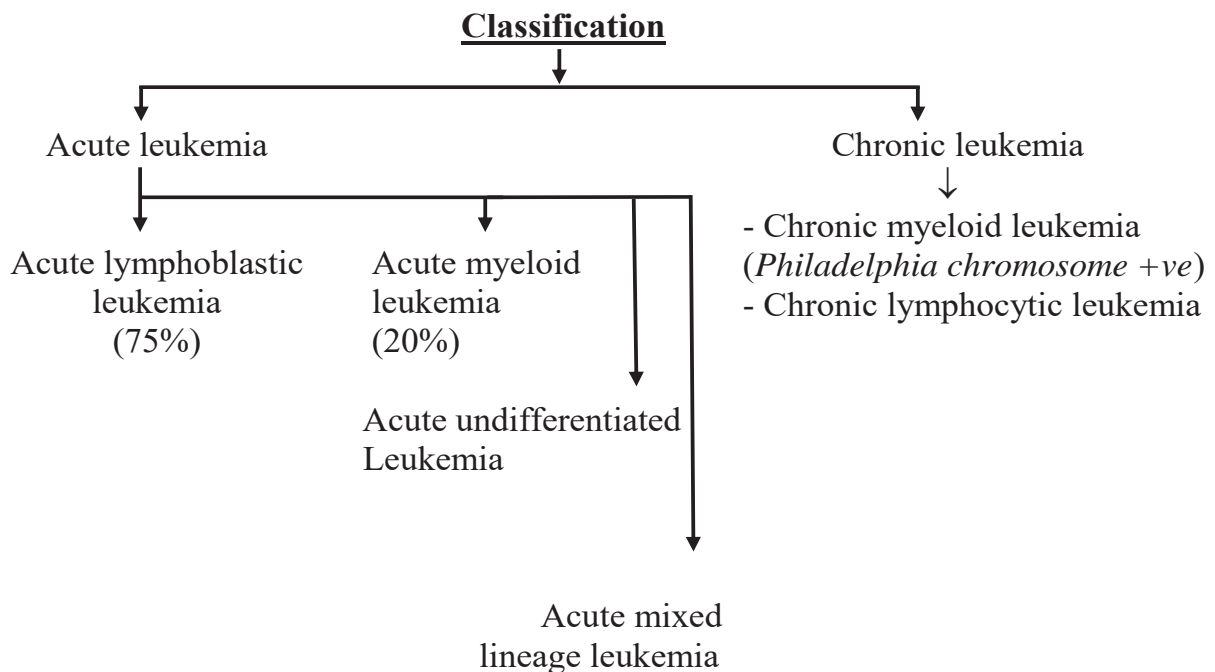
Definition

- Group of malignant diseases of hematopoietic cells in bone marrow
- Giving rise to uncontrolled clonal proliferation of cells
- With arrest of maturation at different stages
- With subsequent marrow failure.

Risk factors

The etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia

- 1- Genetic predisposition
- 2- Chromosomal anomalies e.g. Down
- 3- Chromosomal breakage disorders e.g. Fanconi anemia, Bloom syndrome, ataxia telangiectasia
- 4- Immunodeficiency states
- 5- Ionizing irradiation which either diagnostic irradiation or therapeutic
- 6- Chemical carcinogens: Benzene, Pesticide, Alkylating agents.
- 7- Viral infections



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Acute Lymphoblastic Leukemia (ALL)

Incidence

- Peak age = 2-5 years, more in boys than in girls in all ages.
- Among identical twins, the risk to the second twin if one develops leukemia is greater than that in the general population

Classifications

1. Morphologic: (French – American – British) FAB classification.

L1	L2	L3
85 %	14 %	1%
<ul style="list-style-type: none"> - Small cell - Small cytoplasm - Best prognosis 	<ul style="list-style-type: none"> - Larger cell - Larger cytoplasm - Prominent nucleoli - Poor prognosis 	<ul style="list-style-type: none"> - Large cell - Vacuolated cytoplasm - Worst prognosis.

2. Immunophenotyping

Classify ALL according to blast cell membrane & cytoplasmic markers.

1. Precursor B-cell ALL (CD10+ or common acute lymphoblastic leukemia antigen [CALLA] positive)
 - The commonest ALL: 85 %
 - Best prognosis
2. T cell type
 - Less common : 15 %
 - Poor prognosis
3. B cell type(Burkitt type)
 - least common : < 1%
 - Worst prognosis

Clinical picture

I. The initial presentation of ALL

Usually is nonspecific and relatively brief.

- Anorexia, fatigue, malaise, and irritability
- Intermittent, low-grade fever.
- Bone or, less often, joint pain, particularly in the lower extremities, may be present

II. Manifestations of bone marrow failure

- Anemia (erythroid cell infiltration, bleeding) → pallor
- Thrombocytopenia → purpura , ecchymosis , orificial bleeding.
- Granulocytopenia & granulocytic dysfunction → persistent infections (bacterial, viral, fungal and protozoal) and persisting pyrexia

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III. Manifestations of organ infiltration

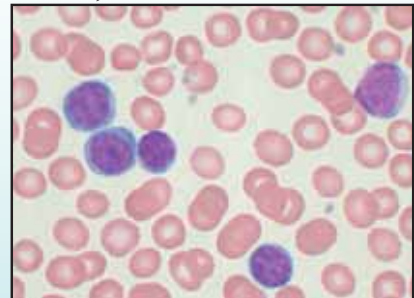
- Generalized lymphadenopathy
- Hepatosplenomegaly (HSM)
- Respiratory distress can occur in patients with an obstructive airway problem (wheezing) due to a large anterior mediastinal mass (e.g., in the thymus or nodes). This problem is most typically seen in adolescent boys with T-cell ALL.
- CNS leukemia: may manifest with:
 - Raised intracranial tension → headache, vomiting, coma or
 - Focal lesion → fits, paresis, cranial nerve paralysis.
- Testis → painless swelling
- Kidneys → hematuria, renal failure
- Bone swellings (infiltration) / Arthritis → limping

Investigations

A. For diagnosis

1. CBC/Blood smear

- WBCs: → Count may be normal, low or high.
→ Blood smear show leukemic blast cells , but absence of blasts doesn't exclude leukemia.
- Platelets: → Thrombocytopenia
- RBCs: → Normocytic anemia.



2. Bone Marrow examination

- Increased cellularity; marrow is replaced by $\geq 25\%$ leukemic blasts cells ; all are having malignant features
- Reduced erythroid and megakaryocytic cells



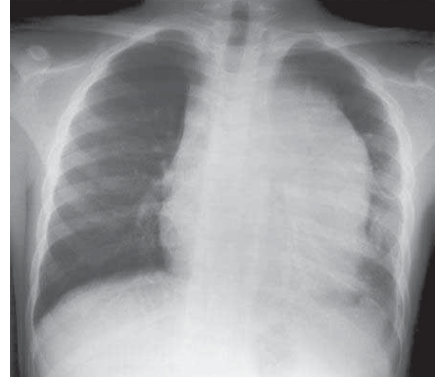
Blast cells must be subjected to:

1. Cytochemistry of blast cells show:
 - Absent peroxidase positive granules
 - Positive periodic acid schiff in clumps.
2. Immunophenotyping.
3. Cytogenetic studies
4. Immunoglobulin and T-cell receptor (TCR) gene re arrangement studies

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B. To detect infiltrations

- Lumbar puncture is done during workup ;approximately 5-10% show leukemic spread to the CSF
- Brain MRI scan
- Chest X-ray:
Mediastinal mass often present in T -ALL



- Abdominal sonogram
- Bone survey for bone infiltration.

C. For planning therapy

- Biochemistry, serum uric acid, renal and liver biochemistry.
- Cardiac function; ECG and Echocardiogram

Differential diagnosis**1. Infections**

Disease	Similarity to leukemia	Exclusion from leukemia
- Typhoid - Brucellosis	- Prolonged unexplained fever	- Blood culture /Serology - Absent blast cells
- Infectious mononucleosis	- Fever - Organomegaly - Purpura	- Absent blast cells - Monospot test - Positive IgM anti EBV
- Perussis	- Fever - Leukemoid reaction (WBCs count $> 50.000/mm^3$).	- No organomegaly - WBCs are mature lymphocytes - Normal blood smear & BM

2. Hematologic /oncologic disorders

	ITP	BM Aplasia	BM infiltration e.g. Neuroblastoma	Hypersplenism
Clinical	- Isolated purpura in clinically well child	- Purpura - Pallor - Pyrexia - No organomegaly	- Purpura - Pallor - Pyrexia - Organomegaly (Abdominal mass)	- Purpura - Pallor - Pyrexia - Splenomegaly
Blood film	- ↓Platelets	- Pancytopenia	- Pancytopenia	- Pancytopenia
Bone Marrow	- Megakaryocyte hyperplasia - No blasts	- Hypoplastic - No blasts	- Infiltrated - Abnormal cells	- Hyperplastic - No blasts

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4. Rheumatologic disease e.g.Rheumatic fever/Juvenile rheumatoid arthritis/SLE

- Cause fever and arthritis/limping
- Other specific clinical features & Lab workup for lupus
- Blood film and bone marrow exclude leukemia

5. Acute myeloid leukemia

- Myeloblasts have: - Peroxidase +ve granules.
- Positive PAS (diffuse reaction).
- Immunophenotyping.
- Cytogenetic studies

Prognosis**Prognostic factors****Clinical**

- Age
- Sex
- Leukemic burden
- Response to therapy

Laboratory

- Initial WBC count
- Immunophenotyping
- Cytogenetics

Risk group	Clinical features	Molecular/genetic features
Low risk	<ul style="list-style-type: none"> - Rapid response to induction therapy - Age 2-10 years - WCC < 50 x 10⁹/L - Precursor B cell phenotype - No central nervous disease - No testicular disease - C-ALL or L1 	<ul style="list-style-type: none"> - DNA index >1.6 - Polyplidy - t(12;21) or some trisomies
High risk	<ul style="list-style-type: none"> - Induction failure ; > 4weeks to remission - Age > 10 years - High minimal residual disease 	<ul style="list-style-type: none"> - Hypopliody - Presence of t(9;22) or t(4;11)

N.B: The single most important prognostic factor in ALL is the response to treatment

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Treatment of ALL

A. Supportive

1. Psychological & nutritional support

2. Control infections by

- Education of patients, relatives and staff about hand washing and isolation facilities and mouth care
- Anti-microbial protocols in case of fever
- Granulocyte colony stimulating factor (G-CSF)

Or

- Granulocyte Monocyte Colony Stimulating Factor (GM-CSF) for granulocytopenia; $< 500 \text{ cell/mm}^3$

- Prophylactic treatment for *Pneumocystis jiroveci* pneumonia

3. Control bleeding by: Platelet transfusion if $< 10\text{-}20,000 / \text{mm}^3$

4. Control anemia by: Packed red cells if hemoglobin falls below 7 gm/dl.

5. Avoid tumor lysis syndrome

- High-count ALL (especially T-cell) and B-cell NHL (specifically Burkitt lymphoma) have the potential for bulky disease – a high cell mass, which will undergo lysis with treatment, resulting in the intracellular contents of potassium, phosphate and nuclear debris being released into the circulation
- Lymphoblast cells have four times the amount of phosphate compared to normal white cells
- Uric acid crystals and phosphate (precipitating out with calcium) crystals may cause acute renal failure and the following:
 - Rise in urate
 - Within 1-2 days; rise in phosphate with concomitant hypocalcaemia
 - Then rapid development of hyperkalemia

Prevention

- Treatment of hyperkalaemia
- Hyperhydration: Intravenous fluids without added potassium
- Alkalinaization prior to chemotherapy
- Uric acid-lowering agents : Urate oxidase (Rasburicase) is the drug of choice or Allopurinol
- Dialysis or hemofiltration



B. Specific treatment

1. Induction of remission

Aim	→ Eradicate malignant cells in bone marrow (i.e. remission).
Duration	→ 4 weeks
Drugs	<ul style="list-style-type: none"> – Vincristine weekly (IV) – Prednisone daily (Oral) – L-asparaginase (IM) – CNS therapy ; see below. – Daunomycin at weekly intervals for patients at higher risk
Criteria of remission: With this approach, 98% of patients are in remission	
* Clinical	→ No organomegaly nor detectable extramedullary disease
* CBC	→ No blast cells in peripheral blood nor in the CSF
* BM	→ Blast cells < 5%; none are having frank malignant features

2. CNS prophylaxis (CNS therapy)

Target patients	Patients who, at the time of diagnosis, have lymphoblasts in the CSF <u>and</u> either an elevated CSF leukocyte count or physical signs of CNS leukemia, such as cranial nerve palsy.
Aim	Prevent later CNS relapses→The likelihood of later CNS relapse is reduced to <5%.
Duration	→ 4 weeks
Drugs	<ul style="list-style-type: none"> – Intrathecal methotrexate. – A small percentage of patients with features that predict a high risk of CNS relapse may receive irradiation to the brain

3. Consolidation and intensification phase

- Aim: Maintain remission and avoid relapse
- Many regimens provide 14-28 wk of multiagent therapy
- Drugs and schedules used vary depending on the risk group of the patient.

4. Maintenance phase of therapy

Aim	→Maintain remission
Duration	→ Lasts for 2-3 yr, depending on the protocol used.
Drugs	<ul style="list-style-type: none"> – Oral 6 mercaptopurine daily . – Intravenous methotrexate weekly. – Usually with intermittent doses of vincristine and corticosteroid.

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C. Bone marrow transplantation

Done in the first remission for high-risk patients such as those with the t(9;22) translocation known as the Philadelphia chromosome or extreme hypodiploidy

Complications**A. Complications of chemotherapy**

- Bone marrow depression → Pancytopenia.
- Vincristine → Neuritis.
- Methotrexate → Renal toxicity.
- Adriamycin → Cardiomyopathy.

B. Relapse

Defined by any of the following

- a- More than 25% lymphoblasts in bone marrow
- or**
- b- Leukemic cell infiltration in the CNS or the testis.

Possible causes

- Persistence of leukemic cells in hidden sites (CNS, testis)
- Drug resistance

Decision

- Intensive chemotherapy and bone marrow transplantation
- Local irradiation

Minimal Residual Disease (MRD)

- Patients in clinical remission can have minimal residual disease (MRD) that can only be detected with specific molecular probes to translocations and other DNA markers contained in leukemic cells or specialized flow cytometry.
- MRD can be quantitative and can provide an estimate of the burden of leukemic cells present in the marrow.
- Higher levels of MRD present at the end of induction suggest a poorer prognosis and higher risk of subsequent relapse.
- MRD of 0.01-0.1% on the marrow on day 29 of induction is a significant risk factor for shorter event-free survival for all risk categories, when compared with patients with no MRD

Acute Myeloid Leukemia (AML)

Other names: Acute Myeloblastic Leukemia, Acute non-lymphoblastic Leukemia

Risk factors

- Chromosomal anomalies e.g. Down, Fanconi anemia, Bloom syndrome.
- Anti neoplastic drugs.

FAB classification

- M0 : Acute myeloblastic leukemia without differentiation
- M1 : Acute myeloblastic leukemia with minimal maturation
- M2 : Acute myeloblastic leukemia with maturation
- M3 : Acute Pro myeloblastic leukemia
- M4 : Acute Myelomonocytic leukemia
- M5 : Acute Monocytic leukemia
- M6 : Acute Erythroleukemia
- M7 : Acute Megakaryocytic leukemia

Clinical picture

- As ALL
- Signs and symptoms that are uncommon in ALL, including
 1. Subcutaneous nodules or "blueberry muffin" lesions (especially in infants)
 2. Chloromas (discrete granulocytic masses):
 - Typically are associated with the M2 with a t(8;21) translocation.
 - Common sites : retro orbital (→ proptosis), skin and epidural space.
 3. Signs and laboratory findings of disseminated intravascular coagulation (especially indicative of M3).
 4. Infiltration of the gingiva (especially in M4 and M5 subtypes)



"Blueberry muffin" lesions



Chloromas



Gingival hypertrophy

Investigation:

- As for ALL
- Bone marrow show myeloblasts which have:
 - Peroxidase positive granules.
 - Positive PAS (diffuse reaction)
 - Some have Auer Rods
- Immunophenotyping and cytogenetic studies of blast cells

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Treatment

- **Unlike ALL ; therapy for AML is**
 - Of shorter duration
 - More intensive
 - Profound bone marrow aplasia (except for M3 subtype) is usually necessary.
 - Require more aggressive supportive care during the lengthy periods of marrow suppression
 - Overall outlook is less optimistic with survival rates reported of 50-70%
- **Induction chemotherapy includes**
 - Commonly used regimens use cytarabine and an anthracycline
 - In combination with other agents such as etoposide and/or thioguanine
- **Hematopoietic stem cell transplantation**
 - The treatment of choice for:
 - High risk cases
 - Refractory cases
 - Relapsed case
 - Matched-sibling bone marrow or stem cell transplantation *after remission* has been shown to achieve long-term disease-free survival in 60-70% of patients
- **Acute promyelocytic leukemia (FAB-M3)**

Characterized by

 - A fusion gene involving the retinoic acid receptor t(15;17)
 - Very responsive to All-Trans-Retinoic Acid ; ATRA (Tretinoin) combined with anthracyclines and cytarabine.
 - ATRA allows maturation of the accumulated promyelocytes
 - The success of this therapy makes marrow transplantation in first remission unnecessary for patients with this disease.

Lymphoma

Definition

Malignant tumors of lymph nodes (LN) and extra nodal lymphoid tissue.

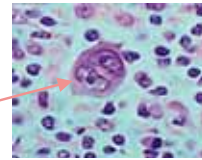
1- Hodgkin disease(HD): Mainly nodal disease

2- Non Hodgkin lymphoma(NHL): Mainly extra nodal disease

Incidence: 13 : million children

Hodgkin Disease

- B-lymphocyte malignancy.
- With characteristic *Reed-Sternberg cells*.
- Peak age → Bimodal; 15-30 and > 60 years ; rare before 5 years.



Histologic classification

Histologic type	Incidence	Criteria
1. Nodular sclerosing	50%	<ul style="list-style-type: none"> - Good prognosis - Females > males - Mediastinal mass common
2. Mixed cellularity	40%	<ul style="list-style-type: none"> - Present with more advanced disease
3. Lymphocyte predominance	10%	<ul style="list-style-type: none"> - Best prognosis
4. Lymphocyte depletion type	Very rare	<ul style="list-style-type: none"> - Present with disseminated disease - Poor prognosis

Clinical picture

1. Lymphadenopathy (Variable size)

Sites	Criteria	Effects
<ul style="list-style-type: none"> - Cervical (75 %) - Supraclavicular - Mediastinal - Mesenteric 	<ul style="list-style-type: none"> - Painless - Rubbery - Discrete - Later become matted and fixed 	<ul style="list-style-type: none"> - Mediastinal syndrome: cough, dyspnea, dysphagia, & facial edema - Mesenteric: - Abdominal mass. - May be intestinal obstruction



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2. B Symptoms

- Unexplained intermittent fever (*Pel-Ebstein* fever).
- Night sweating requiring change of clothes.
- Unexplained loss of body weight > 10% in the last 6 months.

3. Other rare constitutional symptoms and extra nodal involvement

- Fatigue, pruritus, anorexia
- Splenomegaly with or without hepatomegaly.
- Bone marrow failure.

"Modified Ann - Arbor staging"

Based on radiograph and CT of chest, abdomen, and pelvis with or without bone marrow biopsy.

I	Confined to single lymph node region
II	Involvement of two or more nodal areas on the same side of the diaphragm
III	Involvement of nodes on both sides of the diaphragm
IV	Spread beyond the lymph nodes eg liver or bone marrow

Each stage is either

A : Absent of B symptoms

B : Presence of B symptoms

Investigations

A. For definitive diagnosis: Lymph node biopsy

B. For staging

- Chest and abdominal CT scans is the investigation of choice for staging
- Positron emission tomography (PET): Is increasingly being used for staging, assessment of response and direction of therapy

C. Indicators of disease activity

- ESR: is usually raised
- Serum lactate dehydrogenase; raised level is adverse prognostic factor

D. Others

- Chest X-ray may show mediastinal widening, with or without lung involvement
- Liver biochemistry is often abnormal, with or without liver involvement.
- Bone marrow aspirate and trephine biopsy seldom done but show involvement in patients with advanced disease; this is unusual at initial presentation (5%).

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Management

- Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of bulky nodal disease.
- Generally; treatment involves combined chemotherapy with or without low-dose involved-field radiation therapy
- The combination chemotherapy regimens in current use are based on:
 - **COPP** (cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone) **Or ABVD** (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine),
 - For intermediate- and high-risk ; with the addition of prednisone, cyclophosphamide, and etoposide (**ABVE-PC** and **BEACOPP**) or **BAVD** (brentuximab vedotin, doxorubicin [Adriamycin], vincristine, dacarbazine) in various combinations
- Novel promising agents that target RS tumor cells:
 - Anti- CD20 antibody (rituximab)
 - Anti-CD30 agents (Brentuximab)
 - Anti-CD30 antibody linked to the antimitotic agent monomethyl auristatin E Brentuximab vedotin
 - Generated EBV-specific cytotoxic T lymphocytes (CTLs)

Non-Hodgkin Lymphoma

Incidence

- 3 times common than Hodgkin in children
- Peak age around 3 years
- ♂:♀ ratio = 3:1

Aetiology

The cause is unknown.

- Infective agents associated with development of NHL e.g. Epstein Barr virus (Burkitt's lymphoma)
- Diseases known to predispose to NHLs
 - Congenital immunodeficiency states.
 - Acquired immunodeficiency e.g. HIV infection
 - Autoimmune disorders
 - Familial cancer syndromes

WHO Classification

1. B cell lymphoma e.g.
 - Burkitt's lymphoma/leukaemia
 - Precursor B lymphoblastic lymphoma/leukaemia
2. T/NK cell lymphomas e.g.
 - Precursor T cell lymphoblastic leukaemia/lymphoma
 - Diffuse large B cell lymphoma
 - Anaplastic lymphoma

Clinical features

i- Abdominal lymphoma (35%)

- Mainly B cell type; start in Peyer's patches, and mesenteric lymph nodes.
- Presentation:
 - 1- Rapidly enlarging abdominal mass with abdominal pain.
 - 2- May be:
 - Ascites.
 - Hepatosplenomegaly
 - Intussusception.

ii- Anterior mediastinal mass: (25%)

- Mainly T. cell type; starts in thymus.
- Presentation:
 - 1- Mediastinal syndrome (cough, dyspnea, dysphagia, face edema).
 - 2- May be:
 - Pleural effusion.
 - Pericardial effusion.

iii- Others

- Painless lymphadenopathy
- Bone marrow infiltration → pancytopenia (occur in advanced lymphoma).
- CNS infiltration, oropharyngeal involvement, weight loss, bone pain, fever

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Investigations

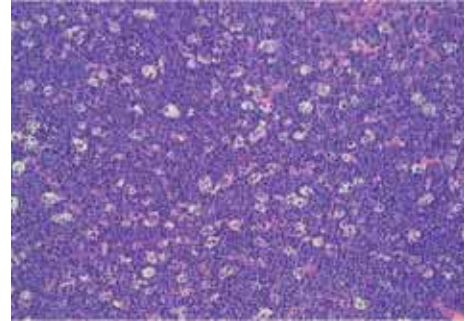
1. Biopsy & immunophenotyping & cytogenetic studies.
2. Cytological examination of ascitic fluid, pleural fluid, B.M
3. Chest X-ray, CT scans of chest, abdomen and pelvis.
4. PET and gallium scans help in staging.
5. Bone marrow aspirate and trephine biopsy are always performed
6. Other investigations as Hodgkin disease

N.B: Burkitt's lymphoma

Nature: B-cell type.

Histology: *Starry sky appearance*

Cytogenetics: May be (t 8; 14).



Types	Endemic	Sporadic
Distribution	African	World wide
Age	Children	Young adults
Site	Jaw, Ovary	Abdomen, Marrow
Association with Epstein Barr virus	In > 97%.	In < 30%.

Treatment

1. **Supportive**; especially for life threatening complications:

Complication	Action
1. Upper airway obstruction by mediastinal mass	- Corticosteroids - Local radiation
2. Tumor lysis syndrome	- Rasburicase - Superhydration. - Na bicarbonate

2. **Surgery**: Only for small, easily, totally resectable tumors.

3. Chemotherapy:

- Protocols combining chemotherapy, Local radiation & CNS prophylaxis
- Protocols differ according to staging (localized or advanced) and Immunophenotyping. It includes:
 - High dose methotrexate (2-3 gm/m²) I.V along with folonic acid
 - Rituximab
 - Targeted irradiation with Rituximab as a carrier
 - Allogeneic hematopoietic stem cell transplantation (HSCT)

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Wilms' Tumor

(Nephroblastoma)

- Embryonic tumor of the developing kidney
- Very good overall prognosis – in excess of 90% 5-year survival rate
- 2nd common abdominal tumor
- 6% of malignancies in children around 3 years.
- Age: usually occurs in children < 5 ys .

Types

1. Sporadic form (common): Usually unilateral.

2. Familial form: Usually bilateral.

3. Associations:

A. Congenital anomalies: in 15 %;

- Genito-urinary anomalies.
- Congenital aniridia .
- Hemihypertrophy e.g. Beckwith–Wiedemann syndrome.

B. Syndromes:

- WAGR syndrome : Wilms', aniridia, genito-urinary anomalies, retardation.
- Denys-Drash syndrome: Wilms'tumor, renal disease, genital anomalies

Clinical picture

Presents in a well child with a painless (or minimal discomfort) abdominal mass, and/or haematuria and/or hypertension (independently or collectively)

1. Abdominal mass (the commonest presentation):

- Never cross midline (enlarged vertically)
- Usually unilateral; Bilateral in 5-10%
- Association: Microscopic hematuria.

2. Hypertension :

- In 60 % of cases
- Due to Renin-producing tumor or renal ischemia.

3. Others: - Polycythemia: occasional .

- Metastasis e.g. Lungs (commonest) → cannon-ball lesions.

Investigations

i. Detect the tumor:

1. Abdominal ultrasonography.
2. Abdominal CT: - Exclude neuroblastoma.
 - Evaluate contralateral kidney.
 - Evaluate metastasis
 - CT guided biopsy.
3. Others: - Urine analysis for hematuria
 - Renal functions tests

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Staging: Based on operative findings

Stage	Tumor extent
I	– Limited to kidney & is completely excised
II	– Extends beyond the kidney but is completely excised
III	– Residual abdominal extension after surgery
IV	– Hematogenous spread to lungs, liver, bone,...
V	– Bilateral renal involvement at time of diagnosis

Differential diagnosis: Causes of abdominal mass

1. Neuroblastoma.
2. Hydronephrosis.
3. Renal cyst.
4. Others: Hypernephroma, Clear cell sarcoma
5. Mesoblastic nephroma

Treatment

1. Surgical: Radical nephrectomy
2. Chemotherapy
3. Radiotherapy

Neuroblastoma

Characters

- Aggressive embryonal tumor of the autonomic system, originating from neural crest-derived sympathetic nerve cells in the adrenal gland & sympathetic ganglia (Abdomen // Thoracic // Cervical)
- Most common cancer diagnosed at age <1 year
- It accounts 8-10% of all childhood malignancies.
- Has the biological potential to involute and resolve spontaneously or behave aggressively with widespread metastases/organ invasion

Staging

Stage	
I	- The tumor is confined to site of origin.
II	- The tumor extend beyond site of origin but not cross midline
III	- Localized tumor with contralateral regional lymph node involvement.
IV	- Metastatic disease .
IVs	- Stage I or II + involvement of skin, liver and/or BM .

Clinical picture

Presenting symptoms are extremely variable

1. Abdominal mass (commonest)

- Origin → adrenal medulla or abdominal sympathetic chain.
- Hard with irregular surface
- Located in upper quadrant of abdomen
- May cross midline as it enlarges horizontally
- May be ascitis , hepatomegaly

2. Mediastinal or cervical mass

- * Origin: Thoracic or cervical sympathetic chain.
- * Manifestations:
 - Mediastinal syndrome: see before
 - Horner syndrome (unilateral ptosis, enophthalmos, meiosis & anhydrosis).

3. Spinal cord compression

- * Origin → sympathetic chain.
- * Manifestations:
 - Localized back pain
 - Paraplegia.
 - Sphincteric dysfunction.

4. Metastatic neuroblastoma

- BM → pancytopenia.
- Orbit→ Proptosis with ecchymotic eye lids → *Raccoon like appearance*.



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5. Syndromes associated with Neuroblastoma

Eponym	Features
Excessive catecholamine	<ul style="list-style-type: none"> Intermittent attacks of sweating, palpitation, hypertension, flushing, polyuria & polydipsia
Horner syndrome	<ul style="list-style-type: none"> Unilateral ptosis, myosis, and anhidrosis associated with a thoracic or cervical primary tumor. Symptoms do not resolve with tumor resection.
Opsoclonus-myoclonus-ataxia syndrome	<ul style="list-style-type: none"> Myoclonic jerking and random eye movement with or without cerebellar ataxia. Often associated with a biologically favorable and differentiated tumor. The condition is likely immune mediated, may not resolve with tumor removal Often exhibits progressive neuropsychological sequelae.
Kerner-Morrison syndrome	<ul style="list-style-type: none"> Intractable secretory diarrhea and hypokalemia due to tumor secretion of vasointestinal peptides. Tumors are generally biologically favorable.

Diagnosis

1. Detect origin of 1^{ry} site (adrenal, sympathetic chain)
 - Abdominal ultrasonography & CT.
 - Chest x ray & CT.
 - Biopsy
2. Urinary catecholamines: Vallinyl mandelic acid & Homovanillic acid

Treatment

- The usual treatment for low-risk neuroblastoma is surgery for stages 1 and 2 and observation for stage 4S with cure rates generally >90%
- Stage 3 : Surgery , radiotherapy and chemotherapy .
- Stage 4 : Radiotherapy or chemotherapy
- Therapies currently under investigation : radiolabeled targeted agents (e.g. MIBG), monoclonal antibodies (anti-tumor-associated GD2) combined with growth factors (GM-CSF), and antitumor vaccines

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Lymphadenopathy

Causes

1. Nonspecific reactive hyperplasia

2. Infection

- A. Bacterial: Staphylococcus, streptococcus, tuberculosis, atypical mycobacteria, Bartonella henselae (cat scratch disease) brucellosis
- B. Viral: Epstein–Barr virus, cytomegalovirus, rubella, rubeola
- C. Protozoal: Toxoplasmosis, malaria
- D. Spirochetal: Syphilis, rickettsia
- E. Fungal: Histoplasmosis, cryptococcus, aspergillosis

3. Connective tissue disorders

- A. Rheumatoid arthritis
- B. Systemic lupus erythematosus

4. Hypersensitivity states e.g. Serum sickness

5. Lymphoproliferative disorders

6. Neoplastic diseases

- A. Hodgkin and non-Hodgkin lymphomas
- B. Leukemia
- C. Metastatic disease from solid tumors: neuroblastoma, nasopharyngeal carcinoma,
- D. Histiocytosis

7. Storage diseases

- A. Niemann–Pick disease
- B. Gaucher disease

8. Immunodeficiency states

9. Miscellaneous causes

- A. Kawasaki disease (mucocutaneous lymph node syndrome)
- C. Sarcoidosis
- E. Hyperthyroidism

Diagnosis

1. Thorough history of

- Infection
- Contact with rodents or cats
- Systemic complaints

2. Careful examination of the lymphadenopathy including

- * All the lymph-node-bearing areas should be carefully examined
- * Size, mobility, warmth, erythema, fluctuation & location.

* Texture of lymph nodes:

- Consistency: soft, firm, rubbery, hard
- Discrete or matted
- Tender (in inflammation or rapid malignancy) or not

3. Physical examination for

- * Draining area in localized adenopathy e.g.
 - Ear, nose and throat in cervical adenopathy
 - Occipital adenopathy in infections of scalp
 - Preauricular adenopathy in conjunctivitis and cat scratch disease
- * Evidence of hematologic disease, such as hepatosplenomegaly and petechiae

4. Workup

- * Blood count
- * Erythrocyte sedimentation rate (ESR)
- * Skin testing for tuberculosis
- * Bacteriologic culture of regional lesions (e.g., throat)
- * Specific serologic tests for e.g. Epstein–Barr virus (EBV)
- * Chest radiograph ± CT scan
- * Abdominal sonogram ± CT
- * LN Ultrasonography
- * Lymph node aspiration and culture
- * Bone marrow examination if leukemia or lymphoma is suspected
- * Lymph node biopsy

Indications

- Initial physical examination and history suggest malignancy
- Lymph node size is greater than 2.5 cm in absence of signs of infection
- Lymph node persists or enlarges
- Appropriate antibiotics fail to shrink node within 2 weeks
- Supraclavicular adenopathy.

Precautions

- Upper cervical and inguinal areas should be avoided
- The largest node should be biopsied, not the most accessible one.
- The node should be removed intact with the capsule, not piecemeal

Splenomegaly

- * Spleen may normally be felt in children up to 3 or 4 years of age
- * At an older age, the spleen tip is generally not palpable below the costal margin and a palpable spleen usually indicates splenic enlargement two to three times its normal size.

Causes of splenomegaly

I. Infectious splenomegaly

- A. Bacterial: acute and chronic systemic infection, subacute bacterial endocarditis, typhoid fever, and miliary tuberculosis
- B. Viral: infectious mononucleosis (Epstein–Barr virus), cytomegalovirus, hepatitis viruses
- C. Spirochetal: Syphilis
- E. Protozoal: malaria, toxoplasmosis, leishmaniasis, schistosomiasis, trypanosomiasis
- F. Fungal infections

II. Hematologic disorders

- A. Hemolytic anemias
- B. Extramedullary hematopoiesis as in osteopetrosis and myelofibrosis
- C. Myeloproliferative disorders (e.g., polycythemia vera)

III. Infiltrative splenomegaly

- A. Nonmalignant
 - 1. Langerhans cell histiocytosis
 - 2. Storage diseases such as Gaucher disease, Niemann–Pick disease, amyloidosis and sarcoidosis
- B. Malignant
 - 1. Leukemia
 - 2. Lymphoma

IV. Congestive splenomegaly: portal hypertension

B. Connective tissue disorders e.g.,

- Systemic lupus erythematosus
- Rheumatoid arthritis

VI. Primary splenic disorders

- A. Cysts
- B. Benign tumors (e.g., hemangioma, lymphangioma)
- C. Hemorrhage in spleen (e.g., subcapsular hematoma)



Pulmonology

To My mother and father
To My wife and kids
uploaded by: Dr.Maged Almansour

Class 14

Acute Pharyngitis

It include acute tonsillitis, pharyngitis or tonsillopharyngitis

Causes

Viral or Bacterial (group A β hemolytic streptococci is the commonest.).

Complaint

- Fever, anorexia and malaise
- Sore throat
- Dysphagia



- Red , congested throat
- Inflamed tonsils with white or yellow exudates
- Enlarged tender lymph nodes on the front of the neck
- Associations
 - Conjunctivitis (Adeno virus)
 - Minute vesicles and ulcers (Coxsackie virus)

Complications

- As that of scarlet fever +
- Mesenteric adenitis (\rightarrow abdominal pain).

Treatment

* Symptomatic for fever.

* Specific: e.g. **10** days course of antibiotic (**5** days for Zithromax)

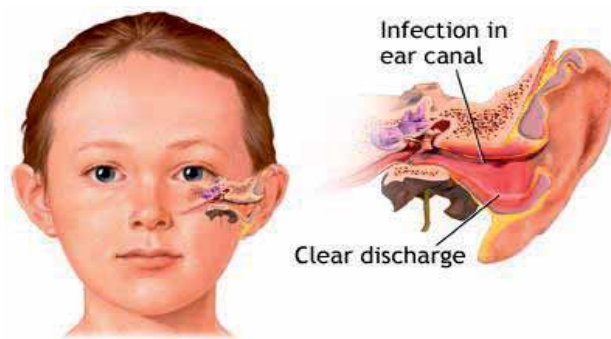
- Penicillin V
- Amoxicillin
- Cephalosporins
- Zithromax
- Clarithromycin

* Surgical:

- A tonsillectomy, with or without adenoidectomy
- Indications:
 1. The most common indication for adenotonsillectomy is adenotonsillar hypertrophy associated with obstructive sleep apnea
 2. Recurrent tonsillitis defined as :
 - Seven or more documented infections in 1 year
 - Five per year for 2 years
 - Or three per year for 3 years
 3. Recurrent peritonsillar abscess
 4. Multiple antibiotic allergies.

Otitis Externa **"Swimmer's ear"**

- Cellulitis of the soft tissues of the external auditory canal
- Risk factors : trauma ,humidity, heat, and moisture in the ear



Essentials to diagnosis

- Edema and erythema of the external auditory canal with debris or thick, purulent discharge.
- Severe ear pain, worsened by manipulation of the pinna.
- Periauricular and cervical lymphadenopathy may be present



Management

- Pain control
- Removal of debris from the canal
- Topical antimicrobial therapy, Fluoroquinolone eardrops are the first-line
- Avoidance of causative factors

Acute Otitis Media (AOM)

Risk factors

Eustachian tube obstruction by adenoids or edema in upper respiratory infection

Others: Impaired host immune defenses, bottle feeding, genetic susceptibility

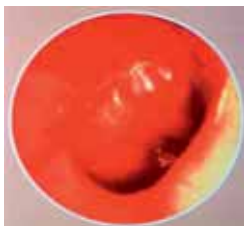
Causes

1. Viral; AOM is a known complication of bronchiolitis

2. Bacterial: mainly H. influenza , pneumococci, moraxilla catarrhalis

Clinical picture

- Fever
- Earache (irritability , rubbing the ears in infants)
- Otoscopic examination:
 - Drum is congested, bulging
 - Middle ear effusion
 - Drum may be perforated ± discharge.



Acute OM



Severe acute OM



Draining acute OM



Resolving acute OM

- Complications:
 - Mastoiditis: tender swelling behind the ear
 - Chronic ear infection: draining ears for 14 days or more

Treatment

* Symptomatic for pain & fever: ibuprofen or acetaminophen

* Specific

- Antibiotic or observation?
 - For infants younger than 6 months→ antibiotics are always recommended on the first visit, regardless of diagnostic certainty
 - For children ≥ 2 years with uncomplicated otitis media without otorrhea→ optional 48 hours of observation
- Antibiotics
 - Amoxicillin-clavulanate enhanced strength ;ES (14:1 ratio of amoxicillin: clavulanate), with amoxicillin dose 90 mg/kg/d for 10 days
 - Alternatives: Ceftriaxone (injections for 3 days), Cefdinir, or Cefpodoxime →Then, according to culture and sensitivity
- Surgical :Tympanocentesis & drainage ± Tympanostomy tubes
- Patients with tympanostomy tubes with acute otorrhea → ototopical antibiotics (fluoroquinolone eardrops) are first-line therapy

Acute Sinusitis

- The maxillary and ethmoid sinuses are most commonly involved. These sinuses are present at birth.
- Major risk factors: Upper respiratory tract infections and immunodeficiency

Causes

- As in otitis media
- Mixed infections

Clinical picture

- * Fever and headache
- * Purulent or mucopurulent nasal discharge & post nasal discharge ⇒ cough
- * Others:
 - Nasal obstruction
 - Halitosis (fetid breath odor)
 - Diminished smell
 - Periorbital edema



Investigations

- Culture and sensitivity of sinus aspirate
- Trans illumination test ⇒ opaque sinus
- Plain X ray skull
- CT skull

Treatment

- Symptomatic for pain & fever (paracetamol)
- Specific:
 1. Antibiotics for a minimum of 10 days or 7 days after resolution of symptoms:
 - High dose amoxicillin or amoxicillin/clavulanate
 - Alternatives
 - Ceftriaxone
 - Cefdinir , Cefpodoxime, Cefixime, Cefuroxime
 - Neither Zithromax nor Cotrimoxazole are recommended
 2. Saline nasal washes or nasal sprays can help to liquefy secretions and act as a mild vasoconstrictor
 3. The use of decongestants, antihistamines, mucolytics, and intranasal corticosteroids has not been adequately studied in children and is not recommended for the treatment of acute uncomplicated bacterial sinusitis
- Surgical = Sinusoscopic sinus surgery for chronic cases

(Nelson Textbook of Pediatric)

Stridor

Definition

Harsh, continuous inspiratory sound due to variable obstruction in upper airways (larynx and trachea); may be associated with hoarseness of voice and respiratory distress

Causes

Acute

Infectious	Non infectious
* Viral: <ul style="list-style-type: none"> – Laryngeotracheobronchitis – Acute laryngitis. – Spasmodic laryngitis. * Bacterial: <ul style="list-style-type: none"> – Acute epiglottitis. – Acute tracheitis (staph. aureus). – Diphtheritic laryngitis. 	<ul style="list-style-type: none"> – Laryngeal foreign body. – Laryngeospasm(e.g. tetany). – Laryngeal edema(e.g. allergic) – Laryngeal compression.

Chronic

Congenital	Acquired
<ul style="list-style-type: none"> ▪ Laryngeomalacia ▪ Laryngeal web or cyst ▪ Tracheomalacia ▪ Congenital vascular ring 	<ul style="list-style-type: none"> ▪ Laryngeal <ul style="list-style-type: none"> – Stenosis – Tumors – Paralysis ▪ Tracheal stenosis

Severity of Stridor / Croup

	Mild	Moderate	Severe
Stridor	±	+	++
Sternal tug	-	+	++
Recession	-	+	++
Accessory muscles	-	+	++
Nasal flare	-	+	++
Cyanosis	-	-	+
Drooling	-	-	+
Air entry	Normal	Reduced	Poor
Hydration	Normal	Normal/reduced	Reduced

If the child does not object:

Saturation	Normal	Normal/reduced	Reduced
Heart rate	Normal	Raised	Raised (bradycardia is pre-terminal event)

(Oxford Paediatric Emergency Medicine)

Acute Infectious Stridor

Laryngotracheobronchitis (Croup)

- Affects children 6 months - 6 years in the fall and early winter
- Cause: Viral
 - Para-influenza types 1, 3
 - Others: RSV, influenza, adenovirus, corona virus
- Presentation
 - Upper respiratory catarrh (Rhinitis, low grade fever)
 - Croupy ,barking, cough
 - Hoarseness of voice
 - Absence of drooling and toxic appearance
- Croup severity:

Can be severe with inspiratory and expiratory stridor and respiratory distress (*substernal & suprasternal retractions*)



- Neck X ray

Steeple sign: Sub glottic narrowing in antero posterior view
- Complication : Rarely; secondary bacterial infection → Bacterial tracheitis

Differential diagnosis

- **Acute laryngitis**
 - Less severe croup (inspiratory stridor)
 - No respiratory distress
- **Spasmodic laryngitis**
 - Viral but may be allergy or psychogenic (afebrile illness)
 - Occurs at midnight
 - Less severe
 - Recurrence is common
- **Acute epiglottitis and acute tracheitis** : see later

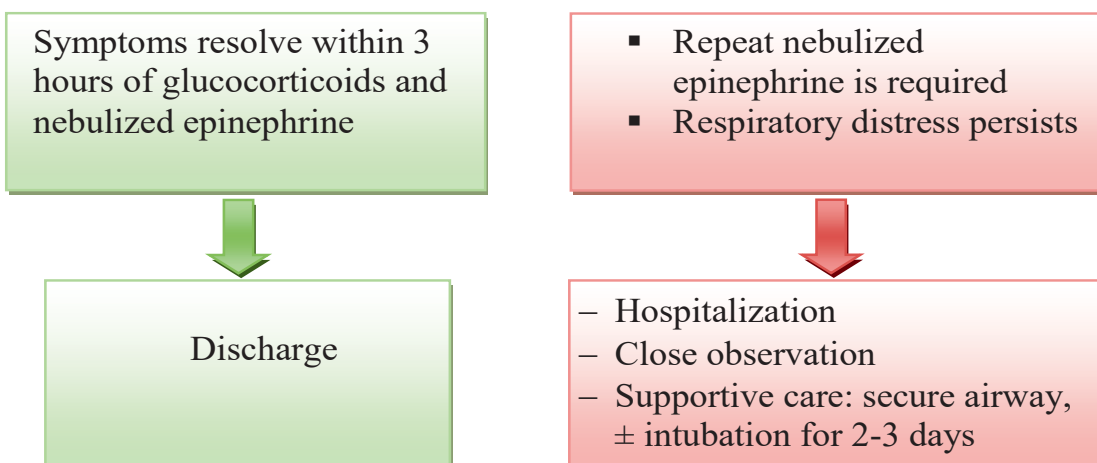
Management

- Most cases respond to home treatment
- **Indication for hospitalization**
 - Progressive stridor
 - Severe stridor at rest
 - Respiratory distress; hypoxia, cyanosis, depressed mental status
 - Poor oral intake
- **Mild croup** (barking cough and no stridor at rest)
 - Oral hydration
 - Minimal handling
 - Mist therapy (no evidence to support its use)
- **Moderate to severe stridor at rest**
 1. Oxygen for patients with oxygen desaturation
 2. Nebulized epinephrine
 - Racemic adrenaline nebulizer (0.25-0.5 ml in 3ml saline),
 - L- adrenaline 5 ml 1:1000 solution is equally effective

Value
Reduce need for intubation for moderate to severe stridor at rest
 3. Oral corticosteroids
 - Dexamethasone: 0.6 mg/kg Oral or intramuscular as one dose.
Lower dexamethasone dose (0.15 mg/kg) is equally effective
 - Inhaled budesonide (2–4 mg)

Value
Improves symptoms even in mild stridor
Reduce need for intubation for moderate to severe stridor at rest

Outcome



(Nelson textbook of pediatrics)

Acute Epiglottitis (Supraglottitis)

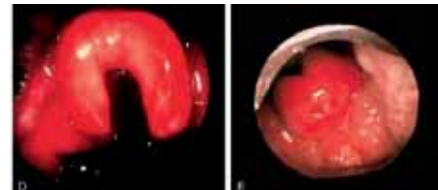
- Infection of the epiglottitis by *Hemophilus influenza type B* (in pre vaccine era)
- *Strept pyogenes*, *Strept pneumoniae*, nontypeable *H. influenzae*, & *Staph aureus*, represent a larger portion of pediatric cases of epiglottitis in vaccinated children

Clinical picture

- Peak age = 2-7 years (now commoner in adults with sore throat)
- Toxic child with high fever
- Drooling of saliva (severe dysphagia)
- The child is severely exhausted :
 - Voice is muffled.
 - Stridor is mild.
 - Little or no cough
 - The child prefer upright posture and neck is hyperextended in an attempt to maintain the airway



- Laryngeoscopic examination shows large "cherry red" swollen epiglottitis but this procedure and any minor procedure may precipitate complete airway obstruction.



Management

Medical emergency, once suspected, the patient must be admitted to the PICU

- Secure the Airway before any maneuver:
 - Endotracheal tube (or less often tracheostomy) is indicated, regardless degree of respiratory distress, placed either in an operating room or ICU
 - The artificial airway is kept in place for 2-3 days
 - O₂ inhalation as needed
- Blood culture and, if possible, epiglottic surface culture should be done.
- Antibiotics:
 - Start parenteral Ceftriaxone or Cefotaxime or Meropenem pending result of culture & sensitivity
 - Continue antibiotics for at least 10 days.
- Lateral X-ray of the neck if done (after securing airway) may show swollen epiglottitis (*Thumb sign*)



N.B: Household contacts < 4 years with incomplete HiB immunization or immunocompromised require Rifampin prophylaxis (20 mg/kg orally once a day maximum dose 600 mg for 4 days)

(Nelson textbook of pediatrics)

Bacterial Tracheitis

- Acute bacterial infection of the upper airway that is potentially life threatening.
- *Staphylococcus aureus* is the commonest cause
- Often follows viral laryngotracheobronchitis
- Commoner than acute epiglottitis basically because of introduction of *Hib* vaccine in most vaccinations protocols √√

Clinical picture

- The early clinical picture is similar to that of viral croup
- Instead of gradual improvement, patients develop higher fever, toxicity, and progressive or intermittent severe upper airway obstruction that is unresponsive to standard croup therapy
- Differentiated from epiglottitis by:
 1. Preceded by viral prodrome
 2. No posture preference; the patient can lie flat
 3. No dysphagia or drooling!!
 4. Lateral neck radiographs show a normal epiglottis but severe subglottic narrowing; irregular tracheal border (absent thumb sign)
 5. During endotracheal intubation/ Bronchoscopy: Normal epiglottis and the presence of deep red mucosa and copious purulent tracheal secretions below the cords confirm the diagnosis
 6. Although cultures of the tracheal secretions are frequently positive, blood cultures are almost always negative
 7. Despite the severity of this illness, the reported mortality rate is very low if it is recognized and treated promptly

Treatment

- Patients with suspected bacterial tracheitis will require
 - Direct visualization of the airway in a controlled environment
 - Debridement of the airway
 - Most patients will be intubated because the incidence of respiratory arrest or progressive respiratory failure and respiratory arrest is high
 - Thick secretions persist for several days, usually resulting in longer periods of intubation for bacterial tracheitis than for epiglottitis or croup
- Antistaphylococcal agents: vancomycin or nafcillin or oxacillin
- Supportive care in ICU including supplemental oxygen ,suctioning

Lower Respiratory Diseases

Chest Examination

	Pneumonia	Bronchopneumonia	Pleural effusion	Pneumothorax	Hydropneumothorax	<u>Collapse</u>
<u>Inspection</u>						
- Movement	Decreased	Decreased bilateral		Decreased		Decreased
- Shape	Normal	Normal		Bulge		Retraction
<u>Palpation</u>						
- Tracheal shift	Central	Central		Shifted to opposite side		To same side
- Tactile vocal fremitus	Increased	? Normal		Decreased		Decreased
<u>Percussion</u>						
- Note	Impaired note	? Impaired note	Stony dull	Hyperresonance	Shifting dullness	Dull
- Topography	Lobar	Bilateral	Rising to axilla	Allover the side	Transverse upper border	Lobar
<u>Auscultation</u>						
- Breath sounds	Diminished bronchial	? Normal vesicular		Markedly diminished vesicular		
- Adventitious sounds	Crepitations	Bilateral wheezes , Crepitations				
- Vocal resonance	Increased Bronchophony	May be normal		Decreased		
<u>Special signs</u>	--	--	Aegophony	Coin test	Succession splash	--

Pneumonia

- Pneumonia is an infection of the lower respiratory tract that involves the airways and parenchyma with consolidation of the alveolar spaces
- Pneumonitis is a general term for lung inflammation that may or may not be associated with consolidation

Anatomic classification

- Lobar pneumonia: pneumonia of one or more lobes
- Bronchopneumonia: scattered bilateral inflammation both lungs
- Interstitial pneumonia: bilateral perihilar pulmonary inflammation

Etiologic classification

Category	Etiologic agents
Bacterial	<ul style="list-style-type: none"> – Gram-positive: e.g. Strept Pneumoniae, group B and A streptococci ,Staphylococcus aureus – Gram-negative: e.g. H.influenzae , Legionella, Klebsiella
Viral	<ul style="list-style-type: none"> – Respiratory syncytial virus (RSV) parainfluenza , influenza , adenovirus, Human metapneumovirus, Corona virus
Atypical	<ul style="list-style-type: none"> – Mycoplasma pneumoniae , Chlamydophila pneumoniae – Chlamydia trachomatis (in infants)
Mycobacterial	<ul style="list-style-type: none"> – Tuberculosis and atypical mycobacteria
Aspiration	<ul style="list-style-type: none"> – Oral anaerobic flora, with or without aerobes
Allergic	<ul style="list-style-type: none"> – Eosinophilic pneumonia (Löffler's syndrome)
Rickettsial	<ul style="list-style-type: none"> – Coxiella Burnetii
Opportunistic in immunocompromised	<ul style="list-style-type: none"> – Fungal e.g. Aspergillus , histoplasma , cryptococcus, candida – Protozoal ; Pneumocystis jiroveci (carinii) – Bacteria; Klebsiella, and proteus

Symptoms

Onset is variable from acute, sub-acute or gradual

- General
 - Fever, malaise , toxemia (worst in bronchopneumonia)
 - May be abdominal pain: Referred from lower lobe pneumonia
- Chest
 - Cough (dry then productive)
 - Dyspnea and grunting

Signs

Respiratory distress

- Tachypnea is the most consistent clinical manifestation of pneumonia, nasal flaring, retractions and grunting
- Cyanosis and lethargy in severe infection specially in infants

Chest examination

- Pneumonia (See table previous page for pneumonia \pm effusion)
- Bronchopneumonia (See table previous page)
- Interstitial pneumonia: \rightarrow Minimal chest findings.
 \rightarrow Prolonged expiration & wheezes are common

Viral or bacterial pneumonia?

1. Clinical

Large pleural effusion, lobar consolidation, and a high fever at the onset of the illness are suggestive of a bacterial etiology

2. Investigations : See later

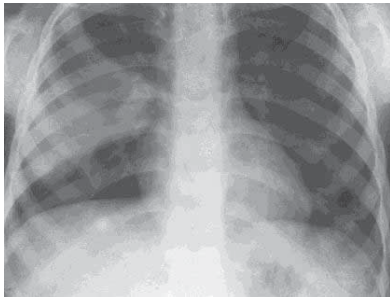
Investigations

A. Radiological

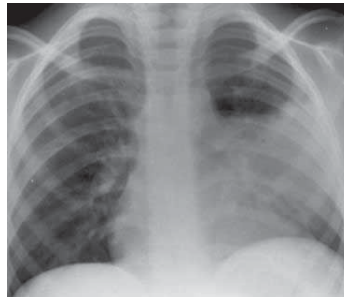
1. Chest X-ray findings:

A. Lobar pneumonia

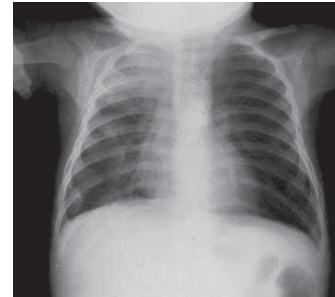
- Homogenous opacity in one or more lobes
- With clear costophrenic angle (differentiate it from effusion)
- Usually bacterial



Right sided middle lobe pneumonia



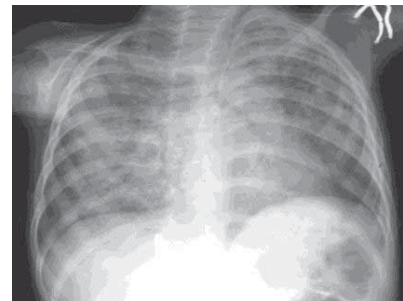
Left sided lower lobe pneumonia



Right sided upper lobe pneumonia

B. Bronchopneumonia

- Scattered opacities in both lungs
- Viral or bacterial



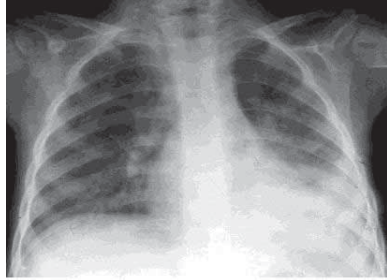
C. Interstitial pneumonia

- Scattered bilateral interstitial infiltrates and peribronchial cuffing
- Hyperinflation, and atelectasis
- Seen in viral bronchopneumonia and atypical pneumonia

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D. Complications

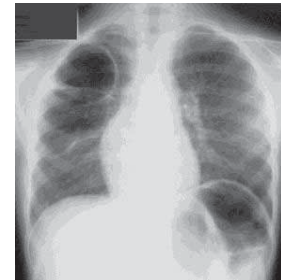
Effusion, abscess, or pneumatoceles (single or multiple, thin-walled, air-filled, cystlike cavities) may indicate *S. aureus*, gram-negative, or complicated pneumococcal pneumonia.



Effusion (Left)



Lung abscess (Right)

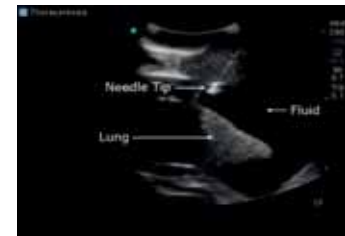


Pneumatoceles (Right)

Meningitis, suppurative arthritis, and osteomyelitis are rare complications of hematologic spread of pneumococcal or H. influenzae type b infection

2. Ultrasonography:

- Highly sensitive and specific in diagnosing pneumonia by determining lung consolidations and air bronchograms or effusions
- Differentiate simple effusion and empyema
- Guide thoracentesis of a loculated effusion



3. Contrast CT scan, CT or ultrasonography guided lung biopsy:

Reserved for complicated cases/ rare pneumonias

B. Laboratory

1- WBC count

- In viral pneumonia usually not higher than $20,000/\text{mm}^3$, with a lymphocyte predominance
- In bacterial pneumonia, in the range of $15,000\text{--}40,000/\text{mm}^3$, and a predominance of granulocytes
- Mild eosinophilia is characteristic of infant *C. trachomatis* pneumonia

2- Acute phase reactants: High ESR, positive C-reactive protein and Procalcitonin *usually* suggest bacterial rather than viral pneumonia

3- Isolation of an organism

Indicated for

- Ill cases that require hospitalization
- Immunocompromised patients
- Patients with recurrent pneumonia
- Pneumonia unresponsive to empirical therapy

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Workup

- Blood cultures are positive in 10% to 20% of bacterial pneumonia
- Pleural fluid culture
- Lung tracheobronchial secretions culture
- Invasive: Bronchoscopy with bronchoalveolar lavage ,brush mucosal biopsy, needle aspiration of the lung, and open lung biopsy
- Specific testing e.g.
 - M. tuberculosis : tuberculin skin test, serum interferon-gamma release assay, or analysis of sputum or gastric aspirates by culture, antigen detection, or PCR
 - Detect the virus or viral antigens by DNA or RNA tests

4- Serology: for rising antibody titers:

- Cold agglutinins in 50% of mycoplasma pneumonia (non specific test).
- ASO titer in streptococcal pneumonia

Complications

Respiratory	Systemic
<ul style="list-style-type: none"> – Pleural effusion – Empyema with or without bronchopleural fistula and pyopneumothorax – Lung abscess – Pneumatocoles – Unresolved pneumonia <p><i>These complications are more common with Staph and Klebsiella pneumonia</i></p>	<ul style="list-style-type: none"> – Meningismus especially with right upper lobe <i>pneumococcal</i> pneumonia – Heart failure – Distant infections e.g. Septicemia, meningitis, pericarditis – Paralytic ileus

Differential Diagnosis of pneumonia**1. Viral pneumonia**

The commonest cause in pre-school children with peak at 2- 3 years

Causes: RSV, parainfluenza (1, 2, and 3) viruses, influenza (A and B) viruses, human metapneumovirus, and adenovirus

Clinically: - Preceding upper respiratory tract infection for several days.
 - Fever & respiratory distress ⇒ milder than bacterial pneumonia.
 - May be widespread wheezes and crepitations.

Diagnosis

- CXR: Bilateral peri hilar infiltrates (bronchopneumonia **or** interstitial pneumonia) ± Hyperinflation.
Pleural effusions, pneumatocoles, abscesses, lobar consolidation, and "round" pneumonias are generally inconsistent with viral disease
- CBC : normal or mildly elevated WBCs with predominant lymphocytes
- Detect the virus or viral antigens by DNA or RNA tests

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2. Bacterial pneumonia

	Pneumococcal*	Streptococcal	Staphylococcal	H. Influenzae*	Klebsiella
Age	Commonest bacterial pneumonia in children	Peak age 3-5 yr.	Peak age below 1 year History : staph skin infection	Peak age below 3 yr	more in immune deficient - Has high mortality
C/P	<ul style="list-style-type: none"> - Moderate - Moderate fever - Usually lobar - Bronchopneumonia is commoner in young infants 	<ul style="list-style-type: none"> - Severe with extreme prostration - High fever - Bronchopneumonia with large pleural effusion 	<ul style="list-style-type: none"> - Severe - High fever - May be bronchopneumonia or lobar or hemithorax - Complications (abscess, empyema, and pneumatoceles, and pneumothorax) 	<ul style="list-style-type: none"> - Insidious onset - Prolonged course over weeks - Usually lobar; involving two or more lobes 	<ul style="list-style-type: none"> - Severe, fulminant - High fever with copious purulent secretions - Usually lobar - Complications as Staph.

* High incidence of penicillin resistance so treat with high doses of amoxicillin (80-90 mg/kg/24 hr) or cefuroxime or 3rd generation cephalosporin

3. Mycoplasma pneumonia (Primary Atypical Pneumonia): Common in school age (5-15 yr)

Clinically

- Severe nonproductive **cough** without significant respiratory distress
- Pharyngitis is common
- Minimal physical signs (walking pneumonia)
- May be chest wheezes and inspiratory crepitations

Diagnosis is mainly clinical.

- Blood: CBC is usually normal, Cold agglutinins may be detected
- Chest X-ray show:
 - Scattered bilateral perihilar pulmonary infiltrates
 - Rarely: Lobar pneumonia ± effusion.

Treatment of pneumonia

i. Supportive

- Bed rest, humidified O₂ inhalation ± restricted I.V. fluids
- Symptomatic treatment e.g. antipyretics for fever
- Treatment of complications e.g. Heart failure.
- Aspiration /drainage for effusion or empyema
- Oral zinc (10- 20 mg/day) is recommended *add-on* in developing countries

ii. Specific treatment

1. Suspected bacterial pneumonia: Antibiotics

- As suggested by clinical picture & chest X-ray
- Based on the presumptive cause and the age
- Antibiotic combination if the cause cannot be detected

Duration: For 10-14 days, 5 days if azithromycin is used

Empirical therapy

Milder cases	– Amoxicillin (50–90 mg/kg/dose) <u>or</u> Cefuroxime or Amoxicillin clavulanate
Hospitalized cases	
▪ Children less than 4 weeks	– IV Ampicillin and an Aminoglycoside
▪ Infants 4–12 weeks of age	– IV Ampicillin for 7–10 days
▪ Older child fully immunized against H. influenzae type B and S. pneumoniae	Yes → Ampicillin or penicillin G.
	No → Parenteral cefotaxime or ceftriaxone
▪ Suspected Staph	– Add vancomycin or clindamycin
▪ Suspected Klebsiella	– Add aminoglycoside
▪ Mycoplasma pneumonia	– Erythromycin or azithromycin or clarithromycin
▪ In adolescents	– Fluoroquinolones may be considered

(Nelson textbook of Pediatrics, 2016)

2. Viral pneumonia

- Antibiotics may be considered as a coexisting bacterial infection exists in 30% of cases
- An appropriate antiviral (e.g. Amantadine, Rimantidine, Osetamivir, Zanamivir) should be considered for the child with pneumonia due to Influenza

Prognosis

- Uncomplicated community-acquired bacterial pneumonia show improvement in clinical symptoms within 48-96 hr of initiation of antibiotics.
- Radiographic evidence of improvement lags behind clinical improvement.
- Causes of none improvement with appropriate antibiotic therapy:

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- Complications, such as empyema
- Obstruction from endobronchial lesions or foreign body
- Bacterial resistance
- Pre-existing Diseases: as causes of recurrent pneumonia***
- Nonbacterial Etiologies such as viruses and aspiration

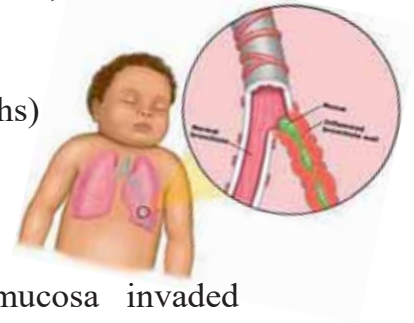
Recurrent pneumonia

- Defined as **2 or more** episodes in a single year **or 3 or more** episodes ever, with radiographic clearing between occurrences
- **Underlying disorder**
 - 1. Hereditary disorders**
 - Cystic fibrosis
 - Sick cell disease
 - 2. Immunodeficiency:** Primary or secondary
 - 3. Disorders of Cilia**
 - Immotile cilia syndrome
 - Kartagener syndrome
 - 4. Anatomic disorders**
 - Aspiration (oropharyngeal incoordination)
 - Gastroesophageal reflux
 - Tracheoesophageal fistula (H type)
 - Foreign body
 - Bronchiectasis
 - Pulmonary sequestration
 - Lobar emphysema

(Nelson textbook of pediatrics)

Acute Bronchiolitis

- Acute inflammation of the bronchioles
- Usually viral infection
 - Respiratory syncytial virus (RSV) in 50% of cases
 - Others: human metapneumovirus, Adenovirus, Para influenza and Mycoplasma
- Incidence
 - Age: The 1st 2 years of life (peak age ~ 6 months)
 - Season: more in winter and spring
 - More in boys who are not breast fed



Pathogenesis

- Viral invasion of small bronchioles mucosa & submucosa invaded
→ acute inflammation → bronchiolar obstruction by edema, mucus and cellular debris
- Impaired pulmonary gas exchange (hypoxemia , hypercapnia) may occur with severe disease

Clinical picture

Symptoms

- Mild upper respiratory catarrh (rhinitis , mild fever) for few days then
- Gradually occurring dyspnea, cough and wheezy chest
- Along with irritability, difficult feeding, air hunger
- Apnea may be more prominent in very young infants (<2 mo old) or former premature infants

Signs

1. Respiratory distress
 - Tachypnea, retractions, grunting ± cyanosis
 - Degree of tachypnea does not always correlate with the degree of hypoxemia or hypercarbia, *so pulse oximetry and noninvasive determination of carbon dioxide are essential*
2. Hyperinflation → Ptosed liver and spleen
3. Chest examination:

Inspection	→ Hyperinflated chest , prolonged expiration
Palpation	→ May be palpable wheezes and decreased TVF
Percussion	→ Bilateral hyper resonance
Auscultation	→ Diminished vesicular breath sounds. → Prolonged expiration. → Bilateral expiratory wheezes → Bilateral fine crackles

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Complications

- Dehydration → due to tachypnea & anorexia
- Lung collapse or pneumothorax → sudden deterioration
- Respiratory failure
- Heart failure

Investigations: Diagnosis of acute bronchiolitis is mainly clinical

- Chest X-ray
 - Indicated only for severe illness or bacterial superinfection suspected
 - Shows:
 - Hyperinflation (horizontal ribs , flat diaphragm)
 - Bilateral perihilar infiltrates ± areas of atelectasis



- Blood tests:
 - ESR, CRP and white blood cell count → are usually normal
 - Arterial blood gases for severe disease
- Detect the virus by cell culture or viral antigen /RNA by PCR using nasopharyngeal aspirate

Differential diagnosis: From other causes of **wheezy** infants e.g.:

- Bronchial asthma: suggested by
 - Recurrent attacks of wheezy chest ± viral prodrome
 - Related to certain allergens or exercise
 - Respond to anti-asthma therapy (bronchodilator trial)
 - Relatives with atopy or asthma/presence of atopy or dermatitis
- Congestive heart failure
- Aspiration syndromes /Foreign body inhalation.
- Cystic fibrosis
- Infections e.g. Pulmonary TB, Pertussis

Treatment

Treat at home or hospital?

Hospitalize if risk factors for severe disease exist e.g.

- Infants younger than 3 months
- Severe respiratory distress or apnea, oral feedings intolerance
- Preterm birth
- Underlying comorbidity

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The mainstay of treatment is:*“Supportive care”*

- Nurse sitting with head and chest elevated at a 30-degree angle with neck extended
- Humidified cool oxygen inhalation with high-flow nasal cannula
- Frequent suctioning of nasal and oral secretions often provides relief of distress
- Care of feeding (more calories are required)
- Parenteral fluids if risk of aspiration exists with respiratory distress
- Treat complications e.g.
 - Antibiotic therapy if secondary bacterial pneumonia suspected
 - CPAP or intubation and mechanical ventilation if deterioration with exhaustion or persistent apnea

Non evidence based and controversial strategies

1. Inhaled bronchodilator*	– Don't modify disease course
2. Steroids*	– Don't modify disease course – Prolong virus shedding
3. Combined nebulized epinephrine* & oral dexamethasone	– Under ongoing studies – Short term relief in severe cases
4. Nebulized hypertonic saline	
5. Heliox	
6. Chest physiotherapy	– Should be avoided
7. Cough sedatives	

* Frequently used

Home oxygen therapy

- Low risk cases that require oxygen can be discharged ER on home oxygen
- Criteria for home oxygen therapy includes
 1. Mild illness as evident by feeding well ,alert and active; minimal retractions; respiratory rate <50 breaths/min, no apnea
 2. Age: 2 mo-2 yr of age with first episode of wheezing during RSV season
 3. Reliable family: good access to healthcare, can manage secretions by bulb suctioning
 4. Absent:
 - Toxic appearance or proven bacterial disease
 - Comorbidities: Cardiac, pulmonary, immunodeficiency, or neuromuscular

(Nelson textbook of Pediatrics)

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Antiviral

Ribavirin aerosol

Indications: risky infants (see later)

Side effect: controversial benefits and very costly

Prevention

- Meticulous hand hygiene is the best measure to prevent nosocomial transmission.
- Monoclonal antibody to RSV F protein (Palivizumab) I.M is given before and during RSV season for *risky infants* < 2 yr of age with:
 - Chronic lung disease
 - Gestational age is less than 35 weeks
 - Comorbidities e.g. congenital heart disease, immunodeficiency, neuromuscular disorders

Prognosis

- The median duration of symptoms is approximately 14 days; the first 2-3 days are the most critical
- Mortality rate \approx 1% due to: apnea , respiratory failure, dehydration
- There is higher incidence of wheezing and asthma in children with a history of bronchiolitis

Bronchial Asthma

Definition

Asthma is a chronic inflammatory condition of the lung airways resulting in airways hyper responsive to various stimuli and episodic airflow obstruction with high degree of reversibility

Incidence

- Boys/ girls: 2:1 before puberty and 1:1 after puberty.
- Most asthmatic children become symptomatic before 5th year

Risk factors/associations

- Parental asthma
- Other allergies e.g. eczema, allergic rhinitis, food allergies
- Rhinitis, sinusitis & gastro esophageal reflux disease (GERD).
- Early weaning from breast milk before 4 months.

Pathogenesis

- Genetic predisposition
- Imbalance between T Helper 1 lymphocytes (Th1) & and T Helper 2 (Th2) with raised Th2 → excessive release of proinflammatory cytokines (IL4, IL5, IL13)
- Exposure to asthma triggers

↓

- Accumulation of IgE in airways and blood (Type 1 hypersensitivity; atopy)
- Increased activated mast cells, eosinophils and chronic inflammatory cells in airways

↓

Bronchoconstriction and airways inflammation with edema, ↑mucus, ↑chronic inflammatory cells

↓

Airways narrowing especially in expiration

- Persistent airway inflammation leads to

↓

- Collagen deposition beneath basement membrane.
- Hypertrophy of muscles & glands.

↓

Airway remodeling and persistent narrowing (Chronic obstructive airway disease (*Cor Pulmonale*))

- Asthma triggers includes

- Respiratory viral infections
- Animals with fur, dust mites, cockroaches
- Aerosol chemicals
- Changes in temperature e.g. early morning
- Drugs (aspirin, beta blockers)

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- Exercise (? Air drafts moving in and out)
- Pollens
- Smoke, tobacco smoke
- Strong emotional expression

Clinical picture

Asthma is strongly suggested with

1. History of any of the following:
 - Cough, worse particularly at night
 - Recurrent wheeze, difficult breathing or chest tightness
2. Symptoms occur or worsen
 - At night, awakening the patient
 - In a seasonal pattern
 - In the presence of a trigger
3. Symptoms respond to short-acting inhaled β -agonist
4. History of other allergies eczema, hay fever,...
5. History of asthma or atopy in other family member
6. History of Patient's colds often "go to the chest" or take longer to clear up

During an attack (Exacerbation)

- Irritability, restlessness.
- Respiratory distress (tachypnea, retractions...)
- **Chest signs**

Chest wheezing (a normal chest examination does not exclude asthma)

Inspection	→	Hyper inflated chest, prolonged expiration and ↓movement Intercostals and subcostal retractions
Palpation	→	Decreased TVF and may be palpable wheezes
Percussion	→	Bilateral hyperresonance with ↓ hepatic & cardiac dullness
Auscultation	→	Diminished vesicular breath sounds with prolonged expiration → Bilateral expiratory wheezes

Types of asthma

1. Transient non atopic wheezing
 - Triggered by common respiratory viral infections
 - Usually resolves during childhood
2. Persistent atopy-associated asthma
 - Associated with atopy
 - Clinical e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy
 - Allergen sensitization, ↑ Ig E and blood eosinophils
 - Tend to persist into later childhood with lung function abnormalities

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Workups in asthma

"Diagnosis of bronchial asthma is mainly clinical"

1. Lung function tests

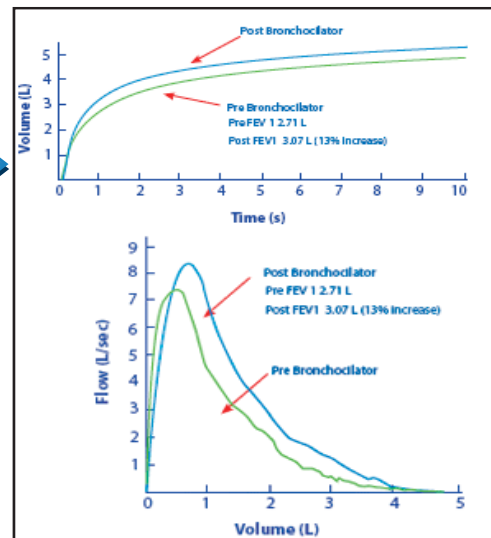
Usually feasible in children > 5 yr of age

A. Spirometry (in clinic)

- FEV1 Forced expiratory volume in the 1st second
- FEV1:FVC ratio Forced expiratory volume in the 1st second/ Forced vital capacity

Findings in asthma

- Low (relative to percentage of predicted norms or previous best)
- Improve after inhaled bronchodilator
- Worsen after exercise challenge



Spirometry is recommended at least annually and more often if asthma is poorly controlled or abnormal lung functions detected

B. Peak Expiratory Flow (PEF)

- Used for home monitoring
- Less sensitive than spirometry



2. Immunologic

- High IgE and eosinophils in the blood and sputum
- Allergen sensitization : Skin testing with suspected allergens

3. Chest X-ray (During exacerbation) may show

- Hyperinflation.
- May detect complications e.g. collapse, pneumothorax

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Treatment

Medications used in bronchial asthma

Reliever medicines

1. Short acting β_2 Agonists (SABA)

- | | |
|--|--|
| <ul style="list-style-type: none"> ▪ Preparations ▪ Action ▪ Duration ▪ Indication ▪ Side effects | <ul style="list-style-type: none"> – Salbutamol – Albuterol – Levalbuterol – Selective β_2 agonists; induce quick and short lived bronchodilatation – Short acting ; 4- 6hrs – Drugs of choice for acute asthma symptoms ("rescue" medication) and for preventing exercise-induced bronchospasm (2.5 – 5 mg by inhalation; dilute with saline to 3 mL) – Tachycardia and tremors (less with Levalbuterol) – Hypokalemia – Overuse of SABAs as a "quick fix" for asthma, rather than using controller medications is associated with an increased risk of death from asthma |
|--|--|

2. Ipratropium bromide

- Parasympatholytic
- Used primarily as add on to SABA in treatment of acute severe asthma
- 125 – 250 microgram by inhalation; dilute with saline to 3 mL
- Useful in wheezing due to bronchmalacia
- Side effects : Mild atropine like / less potent than the β -agonists

Controller medicines

1. Steroids

a. Inhaled corticosteroids (ICS)

- | | |
|--|--|
| <ul style="list-style-type: none"> ▪ Preparations ▪ Action ▪ Indication | <ul style="list-style-type: none"> – Beclomethasone (Qvar) – Budesonide (Pulmicort) – Fluticasone (Flixotide) – Ciclesonide (Alvesco) – Potent anti-inflammatory → reduce airway chronic inflammation and remodeling – ↑↑ expression of β-receptors in bronchial muscles – First-line treatment for persistent asthma – Available in metered-dose inhalers (MDIs), dry powder inhalers (DPIs), or suspension for nebulization |
|--|--|

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- Side effects
 - a. Oral candidiasis (thrush)
 - b. Dysphonia (hoarse voice) due to vocal cord myopathy
 - Both are minimized by:
 - Using a spacer with MDI(reduce oropharyngeal deposition of the drug)
 - Mouth rinsing after ICS use
 - c. ? Steroids systemic effects with high dose, long term ICS

b. Systemic corticosteroids

- Preparations
 - Oral: Prednisolone
 - Parenteral: Methylprednisolone, Hydrocortisone
- Indication
 - Short courses to treat asthma exacerbations
 - Rarely, long courses in patients with severe disease who remain symptomatic despite optimal treatment
- Precaution
 - Children who require routine or frequent short courses of oral corticosteroids, especially with concurrent high-dose ICSs, should receive corticosteroid adverse effects screening and osteoporosis preventive measures

2. Long Acting β_2 Agonists (LABA)

- Preparations
 - Salmeterol (onset after 1hour)
 - Formoterol (onset after 5- 10min→Useful reliever ✓)
- Action
 - Selective β_2 agonist→ prolonged bronchodilatation (12hr)
- Indication
 - add-on agent in asthma suboptimally controlled with ICS therapy alone
- Precaution
 - *LABA should not be initiated as first-line or sole asthma therapy without the concomitant use of an ICS*
 - Should be stopped once asthma control is achieved, and maintain on ICS
- Risks
 - An increase in severe asthma episodes
 - Reported higher number of asthma-related deaths ✓✓

Controller formulations that combine an ICS with a LABA (fluticasone/salmeterol, budesonide/formoterol, mometasone/ formoterol) are available and recommended, in lieu of separate inhaler delivery devices

3. Leukotriene receptor antagonist (LTRAs)

- Preparations
 - Montelukast (Singulaire); chewable tablets or sachets, licensed above 6 months
 - Zafirlukast, licensed above 5 years

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- | | |
|--------------|--|
| ▪ Action | – Leukotriene receptor antagonist with anti-inflammatory and a bronchodilator effect |
| ▪ Indication | – Alternative treatment for mild persistent asthma
– Add-on medication with ICS for moderate persistent asthma
– Reduce exercise-, aspirin-, and allergen-induced bronchoconstriction. |
| ▪ Precaution | – Less effective than ICSs in patients with mild persistent asthma |
| ▪ Risks | – Montelukast has rarely been associated with mood changes and suicidality |

4. Theophylline

- | | |
|--------------|---|
| ▪ Action | – Phosphodiesterase inhibitor → bronchodilatation and anti-inflammatory |
| ▪ Use | – Alternative monotherapy controller agent for older children and adults with mild persistent asthma
– It is no longer considered a first-line agent for young children |
| ▪ Precaution | – Narrow therapeutic window; therefore, when it is used, serum theophylline levels need to be routinely monitored |
| ▪ Overdose | – Headaches, vomiting, cardiac arrhythmias, seizures, and death |

5. Sodium cromoglycate

- Mast cell stabilizer
- Inhibit exercise-induced bronchospasm, they can be used in place of SABAs, especially in children who develop unwanted adverse effects with β -agonist therapy (tremor and elevated heart rate).
- Not a preferred controller ; must be administered frequently (2-4 times/day) and are not nearly as effective daily controller medications

Asthma medicines delivery systems



Metered dose inhaler with a spacer



Dry powder inhaler with metered dose turbobaler

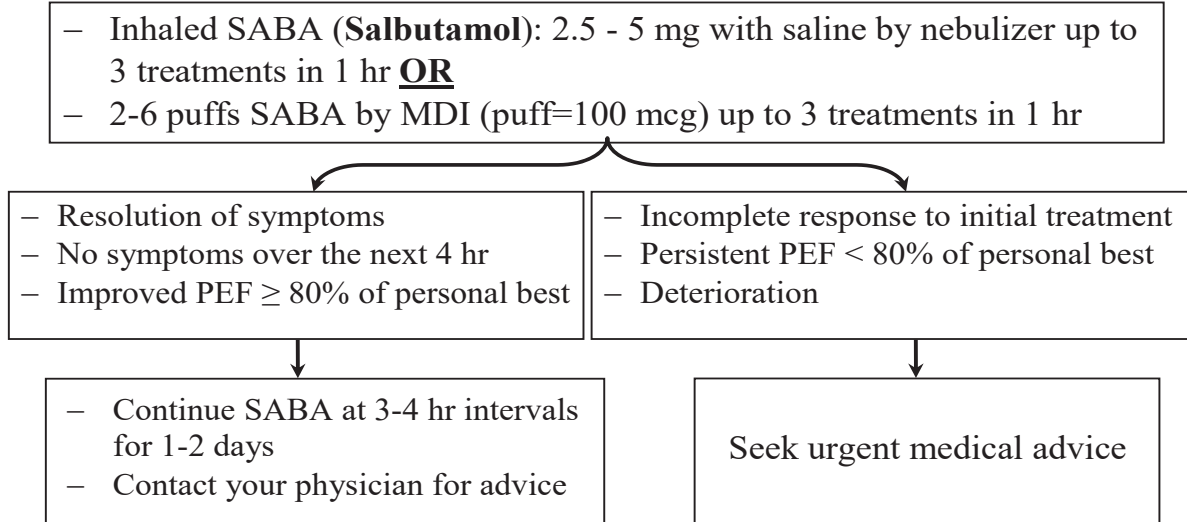


Solution for nebulization

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Management of acute asthma exacerbation

A. At Home



B. Emergency department treatment

Assessment of severity

	Mild	Moderate	Severe
▪ Altered consciousness	Absent		Agitated, confused
▪ Cyanosis	Absent		Likely present
▪ Dyspnea	On walking	On talking	At rest
▪ Speaks	In sentences	Phrases	In words
▪ Pulse	Normal	Mild tachycardia	Marked tachycardia ($> 180\text{bpm}$ in young)
▪ Pulsus paradoxus	Normal	Less than 20 mmHg	20-40 mmHg
▪ Wheezes	End expiratory	Holo expiratory	Exp and inspiratory May be quiet
▪ Retractions	Absent	Common	Usual
▪ Peak expiratory flow	$\geq 70\%$	40-69%*	$< 40\%*$
▪ Oximetry in air	$> 95\%$	90 -95 %	$< 90\%$
▪ PaCO ₂	$< 42\text{ mmHg}^*$		$> 42\text{ mmHg}$
▪ PaO ₂ *	Normal*		$< 60\text{ mmHg}$

* Means test not usually necessary

Signs of acute severe asthma with imminent respiratory arrest

- Drowsy or confused
- Paradoxical thoracoabdominal movement
- Absence of wheeze
- Bradycardia, Absent pulsus paradoxus (due to respiratory muscle fatigue)

Status asthmaticus : A severe asthma exacerbation that does not improve with standard therapy

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Action plan

- Pulse oximetry in air
- High flow oxygen to keep O₂ saturation > 92%
- **SABA (Salbutamol):** 2.5 - 5 mg with saline by nebulizer or 2 to 6 puffs by MDI plus spacer
(Repeat every 20 minutes for the 1st hour)
- **Ipratropium bromide:** 125 - 250 mcg by nebulizer; if no adequate response to the first salbutamol nebulizer
(Repeat every 20 minutes for the first hour only)
- Oral **Corticosteroids** (1-2mg/kg in divided doses) in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms
- **Epinephrine(1:1000) :**0.3-0.5 mg IM or SC may be given in severe cases

Outcome at 1 hour**Good outcome:**

- Normal physical findings
- PEF >70% of predicted or personal best
- Oxygen saturation >92% in room air for 4 hr

1. Wean gradually → SABA every 3-4 hr
2. If on a controller drug (ICS) → continue it during and after exacerbation
3. Continue oral steroids for 3-7 days

- Moderate to severe exacerbations that do not adequately improve within **1-2 hr** of intensive treatment
- High risk patients*

Admission

*** High risk patients include:**

- Previous severe asthma exacerbation (intensive care unit admission)
- Two or more hospitalizations for asthma in past year
- Three or more emergency department visits for asthma in past year
- Low birthweight
- Poverty

(Nelson Text Book of Pediatrics, 2016)

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C. Admission to hospital /PICU

- Admission to an PICU is indicated for patients with
 - Severe respiratory distress
 - Concern for potential respiratory failure and arrest

Action plan

- Cardio-pulmonary monitoring
 - Oxygen
 - **Salbutamol**
 - Nebulizer every 20 min as needed, then every 1-4 hr as needed
 - Or
 - Continuous nebulization with oxygen: 5-15 mg/hr
 - **Corticosteroids:** Short course 3-7 days
 - Oral: Prednisone 1-2 mg/kg
 - Parenteral: Methylprednisolone or Hydrocortisone
- Ipratropium bromide nebulizer (poor evidence; no longer recommended)



Persistent severe dyspnea and high-flow oxygen requirements



- Obtain IV access, take electrolytes , glucose and ABG
- CXR in life threatening attack or suspected pneumothorax (deteriorate after a period of improvement)
- Start IV maintenance fluids
 - Dextrose 5% in 0.45% saline with 20-mmol/l kcl
 - At 70-80% of maintenance
 - Correct any dehydration
- Replace nebulizer by IV **Salbutamol** ; Watch for low potassium and ECG monitoring for arrhythmias



Critically ill or at risk for respiratory failure

Available options

- **Epinephrine** IM or SC
- **Magnesium sulphate** (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 min)
- **Aminophylline** ; loading dose 5-10 mg/kg over 1 hour followed by maintenance 1 mg /kg/hour (0.7 mg /kg/hour if >10 years)
- Inhaled heliox (helium and oxygen mixture)
- Assisted /mechanical ventilation

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After exacerbation resolution:

1. Space SABA gradually
2. Continue steroids for full 3-7 days
3. Start controller therapy
4. Families of all children with asthma should have a written action plan to guide their recognition and management of exacerbations
5. With history of life-threatening episodes, especially if abrupt-onset in nature, providing an epinephrine autoinjector and, possibly, portable oxygen at home should be considered

(Nelson Text Book of Pediatrics, 2016)

Long term asthma management

1. Assessing asthma severity and initiating treatment (For patients who are not currently taking long-term control medications)

		Persistent		
	Intermittent	Mild	Moderate	Severe
1. Daytime symptoms (Wheezing, cough, breathless)	≤ 2 days/wk	> 2 days/wk but not daily	Daily	Throughout the day
2. Nocturnal symptoms /awakening (Nocturnal cough, wheezing, breathless)				
Age < 5 yr	0	1-2 /mo	3-4 /mo	>1 /wk
Age ≥ 5 yr	≤ 2 /mo	3-4 /mo	>1 /wk	Often 7 /wk
3. Need for reliever	≤ 2 days/wk	> 2 days/wk	Daily	Several times per day
4. Limitation of activities (Cough , wheeze, or breathless on exercise, play or laugh)	None	Minor limitation	Some limitation	Extreme limitation
5. Lung function (FEV1); age ≥5 yr	> 80% predicted	≥ 80% predicted	60-80% predicted	< 60% predicted
Recommended step for initiating therapy	Step 1	Step 2	Step 3	Step 3 or Step 4

II. Stepwise Approach for Managing Asthma in Children

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
<i>Rescue treatment for all steps: As needed inhaled short acting β_2 agonist (SABA) \pm Short course of oral steroids if exacerbation is severe or history of previous severe exacerbations</i>					
Move to step 2 if : Rescue treatment is needed more than twice a week or If night-time symptoms at least once a week or If exacerbation in the last 2 years	Low dose ICS Or Montelukast	Medium dose ICS	Medium dose ICS + Montelukast* OR Medium dose ICS + LABA	High dose ICS + Montelukast* OR High dose ICS + LABA	High dose ICS + Montelukast* OR High dose ICS + LABA + Oral glucocorticoids lowest dose
		OR Low dose ICS + Montelukast*			
		OR			
		Low dose ICS + LABA			
Modified-release oral theophylline may substitute Montelukast					
				Consider Anti IgE (Omalizumab) for patients above 12 years with Allergies	
Consider subcutaneous allergen immunotherapy for patients who have allergic asthma					
Patient education, environmental control, and management of comorbidities					

* For those less than 4 years



*Step Down or Step Up gradually
According to assessment of current clinical control (See next table)*



III. Assessment of current clinical control (preferably over 4 weeks)

Characteristic	Well controlled (All of the following)	Not well controlled (Any measure in any week)	Very poorly controlled
Daytime symptoms	None or < 2 /week; very short	>2 days/wk	Throughout the day
Nocturnal symptoms /awakening Age < 5 yr Age ≥ 5 yr	≤ 1 /mo ≤ 1 /mo	> 1 /mo ≥ 2 /mo	>1 /wk ≥ 2 /wk
Limitation of activities	None	Some limitation	Extreme limitation
Need for reliever	≤ 2 days/wk	> 2 days/wk	Several times per day
Lung function (FEV1 or PEF)	> 80% predicted	60-80% predicted	< 60% predicted
Exacerbations requiring systemic steroids courses	0-1/yr	≥ 2/yr	> 3/yr

Action

Step Down gradually to the least medication necessary to maintain control if asthma is well controlled at least 3 months

Step Up gradually after checking inhaler technique, adherence, environmental control, and comorbid condition
Improvement should be seen within 4-6 weeks

IV. Avoid exposure to triggering agents

- Eliminate or reduce problematic environmental exposures
 - Avoid drugs, foods, and additives known to cause symptoms.
 - Avoid allergens as suggested by skin testing
- Treat co-morbid conditions: sinusitis, GERD and rhinitis.
- Give annual influenza vaccine unless egg allergic
- In exercise induced asthma give:

SABA inhalation	→ 10 minutes before exercise
or Montelukast oral	→ 1 hour before exercise

V. Patient education

- Explain basic facts about asthma
- Written asthma management plan
- Demonstrate optimal technique of use of asthma devices
- Insist on adherence to medications
- Ensure avoidance of risk factors
- *Two to four asthma checkups per year for:*
 1. Frequency of asthma symptoms during the day, at night, and with physical Exercise
 2. Frequency of "rescue" SABA medication use and refills
 3. Lung function measurements (spirometry) for older children at least annually
 4. Number and severity of asthma exacerbations
 5. Presence of medication adverse effects since the last visit

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Differential diagnosis of asthma (Wheezy Chest)

Definition of wheeze

- Expiratory musical continuous sound
- Due to partial obstruction of small bronchi & bronchioles
- Can be sibilant or sonorous
- May be also inspiratory in severe obstruction

Possible mechanisms

- Bronchoconstriction (spasm of airways smooth muscles)
- Bronchial mucosal edema.
- Excessive, viscid secretions inside airways lumens

Causes

Acute	Chronic /recurrent
<ul style="list-style-type: none"> ▪ Acute bronchiolitis. ▪ Bronchial asthma exacerbation ▪ Foreign Body inhalation ▪ Congestive Heart failure(e.g. congenital heart diseases or cardiomyopathy) ▪ Aspiration e.g. GERD 	<ul style="list-style-type: none"> ▪ Bronchial asthma ▪ Congestive heart failure ▪ Cystic fibrosis ▪ Dynamic airway collapse: e.g. bronchomalacia & tracheomalacia ▪ Recurrent aspiration e.g. <ul style="list-style-type: none"> – GERD – Tracheo esophageal fistula – Neuromuscular disorders – Foreign body ▪ Pulmonary tuberculosis(LN+) ▪ Airway compression by: lymph nodes, vascular ring or tumor

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Foreign body aspiration

Clinical picture

Squeals

1. Immediate expelling by cough reflex
2. Retained foreign body: manifestations differs according to site

Type of obstruction	Laryngeal	Tracheal	Bronchial
Partial	<ul style="list-style-type: none"> - Respiratory distress - Stridor - Hoarsness of voice - Aphonia 	<ul style="list-style-type: none"> - Metallic cough 	<ul style="list-style-type: none"> - Chest wheezes
Complete	<ul style="list-style-type: none"> - Suffocation 	<ul style="list-style-type: none"> - Respiratory distress - Cyanosis 	<ul style="list-style-type: none"> - Collapse - Abscess - Pneumonia

History

- Commonly reported in children 3 months to 6 years
- History of sudden choking or frank history of foreign body aspiration
- Triphasic history may be obtained:
 - Initial phase: cough, choking, stridor or gagging
 - Silent phase: if foreign body pass and impact in smaller airways
 - Phase of complications: recurrent pneumonia , abscess, bronchiectasis

Signs

- Fixed localized wheeze; unresponsive to treatment.
- Unexplained lung collapse
- Diminished breath sound over one lung, one lobe **or** one segment
- Mediastinal shift (unilateral collapse or emphysema).
- "Same site" recurrent pneumonia, abscess, bronchiectasis

Chest X-ray

- Positive only in about **50%** of cases
- May show obstructive collapse **or** obstructive emphysema in expiratory film.

Treatment

A. Without respiratory distress→ bronchoscopic extraction

B. With respiratory distress:

1. If the child is breathing well:

- Encourage cough to clear the foreign body
- Be vigilant for any deterioration

2. If cough becomes ineffective:

- Try to assist expulsion of the foreign body
- Provide rescue breathing in between trials.



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- Use the Alert, Verbal, Pain, Unresponsive pediatric scoring system (AVPU) to determine both a child's level of consciousness and cerebral cortex function
- If trials fail and infant becomes unconscious, attempt to visualize foreign body and remove manually.

i. First aid for the choking infant < 1 year of age

- Hold infant prone with the head down.
- Give 5 interscapular back blows, using heel of hand.
- Turn the infant supine, with head dependent and perform 5 quick downward chest thrusts.



ii. First aid for the choking child older than 1 year of age

A) In conscious patient ⇒ abdominal thrust in sitting or standing (Heimlich maneuver):

- Encircle the child chest with arms from behind.
- Place one fist against patient's abdomen in midline just below tip of xiphoid.
- Grasp fist with other hand and exert 5 quick, upward thrusts.



B) In unconscious patient ⇒ abdominal thrust in lying down:

- Place the patient supine.
- Open patient airway using chin lift or jaw thrust.
- Place heel of one hand on child's abdomen just below costal margins.
- Place the other hand on top of the first hand.
- Press both hands into abdomen with quick, upward thrusts in midline.



iii. Further interventions

- Laryngoscopic removal.
- If failed; push foreign body more distally.
- If failed, perform immediate cricothrotomy

Prevention

Avoid choking materials in infants and young children e.g. small toys, nuts, popcorn

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Dry Pleurisy

Definition: Fibrinous inflammation of the pleura.

Causes

- Infections: Viral pneumonia, bacterial pneumonia, tuberculosis
- Chest wall trauma
- Collagen diseases e.g. Rheumatic fever, systemic lupus erythematosus

Clinical picture

- Manifestations of **the cause**
- Chest pain: Stitching, ↑ with deep respiration, cough & sneezing
- Patients may prefer to lie on same side.
- Auscultation: *Pleural rub*: - Scratchy sound.
- Decrease by holding breathing.

Treatment: - Treat the cause.
- Analgesics.

Serofibrinous Pleurisy (Pleural Effusion)

- Normally, only 4-12 mL of fluid is present in the pleural space, but if formation exceeds clearance, fluid accumulates.
- Definition: Serofibrinous inflammation of the pleura.

Types of effusion

Transudate	Exudate	Bloody	Cheyulous
<u>Characters</u> <ul style="list-style-type: none"> - Clear; straw colored - Proteins < 3gm/dl - ↓ Cells (mesenchymal) - ↓ Specific gravity - Sterile - ↓ Lactate dehydrogenase 	<ul style="list-style-type: none"> - Turbid ; opaque - > 3 gm/dl. - ↑ Cells (PMNLs) - ↑ Specific gravity (>1015) - May reveal organisms - Lactate dehydrogenase >200 iu /l 	Bloody with RBCs on mic. examination	<ul style="list-style-type: none"> - Milky white - Dissolved with ether - Spread on filter paper
<u>Mechanisms</u> <ul style="list-style-type: none"> - Increased hydrostatic capillary pressure - Decreased plasma osmotic pressure 	Increased capillary permeability due to inflammation , malignancy, mediastinal or chest wall diseases		Impaired lymphatic drainage
<u>Causes</u> Passive transudation in renal, cardiac & hepatic causes of generalized edema	<ul style="list-style-type: none"> - Pneumonia. - T.B. - Ruptured Lung abscess - Mediastinitis - SLE, uremia, metastasis - T cell lymphoma. 	<ul style="list-style-type: none"> - Tumors - Trauma - Hemorrhagic blood Diseases 	Thoracic duct obstruction or trauma

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Clinical picture

Symptoms

- Manifestations of **the underlying cause** (e.g. fever, dyspnea,.....)
- Respiratory distress
- Chest pain: dull aching pain; patient prefers to lie on the affected side

Chest examination

Small effusion:

Clinical picture of an underlying cause e.g. pneumonia →
bronchophony, bronchial breathing and crepitation

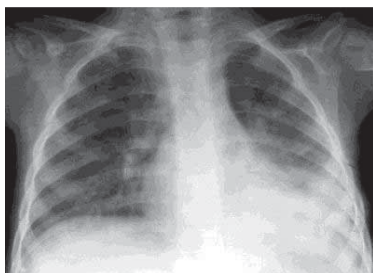
Massive effusion

- Inspection → Unilateral bulge, full intercostal spaces with diminished movement
- Palpation → Decreased TVF & trachea shifted to opposite side
- Percussion → Stony dullness, rising to axilla
- Auscultation → Marked diminished breath sounds (or absent).
→ Aegophony (nasal tone of voice) may present at the top of effusion due to kinked bronchi

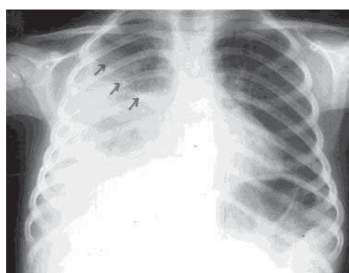
Investigations

1. Chest X-ray in supine and upright positions:

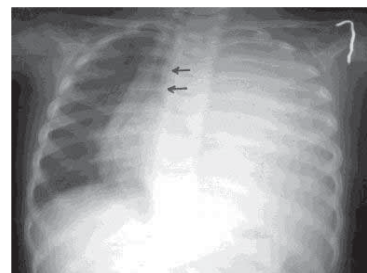
- In small effusion: homogenous opacity just obliterating costophernic angle
- In moderate to large (Massive) effusion: homogenous opacity
 - Filling the costophernic angle
 - Rising to the axilla.
 - With shift of the mediastinum to the opposite side



Mild left sided effusion



Moderate right sided effusion



Massive left sided effusion

2. Chest ultrasonography

- Diagnostic for pleural fluid
- Guide thoracentesis/ Chest tube insertion



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3. Thoracentesis:**a. Inspect the fluid:**

- Straw colored → Transudate
- Turbid → Exudates
- Milky white → Chylous
- Fetid odor → Anaerobic infection , empyema

b. Cytology:

- Polymorph → Infection e.g. Pneumonia , early TB
- Lymphocytes → TB, chylous , malignancy ; lymphoma
- Eosinophils → Parasitism, emboli
- Red cells → Trauma, tumors,.....

c. Order culture & sensitivity**d. Biochemical examination: Mention from previous table****4. Tests for TB:** tuberculin test, sputum analysis and culture**5. Pleural biopsy, thoracoscopy and/ or bronchoscopy:** if TB or malignancy is likely**Outcome of effusion**

- Massive effusion may impair cardiac function
- Secondary pyogenic infection → empyema
- Organization of unresolving exudates may lead to fibrothorax

Treatment**1. Treat the cause****2. Thoracocentesis is both diagnostic and therapeutic****3. Thoracostomy tube drainage**

- Closed drainage using intercostal tube with underwater seal
- Indicated for:
 - a. Massive effusion
 - b. Marked respiratory distress
 - c. Effusion not resolved with medical treatment
 - d. Empyema
- Site of aspiration → 5th space mid axillary line
- Precaution: Rapid removal of ≥1 L of pleural fluid may be associated with the development of re-expansion pulmonary edema

Purulent Pleurisy (Empyema)

Definition

- Exudative pleural effusion with marked ↑↑ pus cells
- "Effusion is empyema if bacteria are present on Gram staining, pH is < 7.20 , and there are $>100,000$ neutrophils/ μL "

Causes

- Pneumonia (Pneumococci, Staph, H. influenza and klebsiella).
- Rupture lung abscess.
- Rupture abdominal abscess or subphrenic abscess
- Rupture of chest wall abscess
- Secondary contaminated chest trauma or surgery
- Secondary infection of an effusion
- Secondary to infection from suppurated lower cervical lymph nodes

Clinical picture

1. Acute empyema: Same as pleural effusion with:

- High fever, toxic patient.
- Same side chest wall edema
- High incidence of complications.

2. Chronic empyema; empyema lasting for 3 months or more:

Clinical	Laboratory
<ul style="list-style-type: none"> – Pale clubbing – Pallor – Low grade fever (Pyrexia) – Eventual fibrothorax ,collapse, with same side mediastinal shift , scoliosos and narrow ribs – Risk of amyliodosis 	<ul style="list-style-type: none"> – Anemia of chronic illness ; normocytic normochromic – Elevated ESR – Poly morph nuclear leucocytosis

Complications

1. Local spread to:

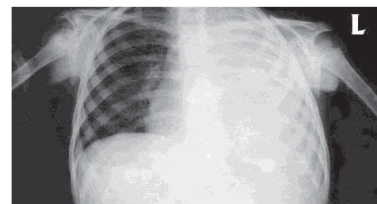
- Lung → Bronchopleural fistula.
- Abdomen → peritonitis.
- Chest wall → empyema necessitatis.
- Pericardium → purulent pericarditis.

2. Distant spread e.g. Meningitis, septicemia,.....

Investigations

1. **Chest X-ray:** as effusion but;

- Opacity is denser.
- Ribs crowding
- May be lung collapse in chronic cases



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2. Thoracocentesis

- For character of the fluid (exudate with ↑↑ pus cells).
- For culture & sensitivity.

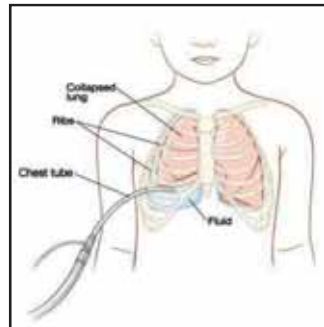
3. Ultrasonography or CT chest: Detect pleural fluid *septa* and loculated empyema

4. Blood cultures: have a higher yield than cultures of the pleural fluid.

Treatment

1. Thoracostomy tube drainage

- Closed drainage using intercostal tube with underwater seal (Open drainage may be necessary in chronic cases)
- For about 1 week
- More than one tube may be needed to drain pockets of pus.
- Use intra pleural fibrinolytic agents (Streptokinase or Urokinase):
 - For 3-5 days
 - Promote drainage, decrease fever, and shorten hospitalization
 - Precaution: risk of anaphylaxis, and hemorrhage



2. Antibiotics: According to culture and sensitivity for 2- 4 weeks

3. Surgical decortications

- Via video-assisted thoracoscopic surgery (VATS) or open thoracotomy
- Indicated for child who remains febrile and dyspneic >72 hr after initiation of therapy with intravenous antibiotics and thoracostomy tube drainage



N.B: Pseudochyolous effusion: Chronic serous effusion with cellular degeneration:

- Criteria:
- High cholesterol /Low triglycerides level.
 - Doesn't clear with ether or alkali.
 - Doesn't spread on filter paper

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Hydropneumothorax

Definition: Presence of both fluid & air in the pleural cavity.

Causes

- Thoracocentesis for pleural effusion → hydropneumothorax.
- Thoracocentesis for hemothorax → hemopneumothorax.
- Empyema with bronchopleural fistula → pyopneumothorax

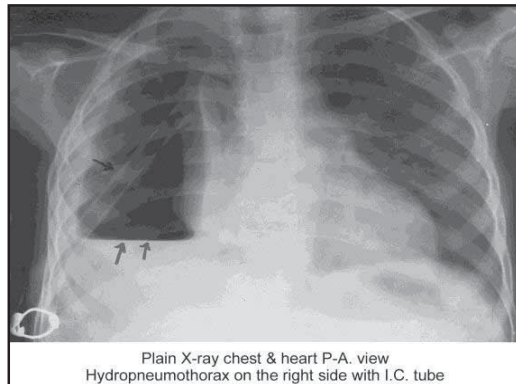
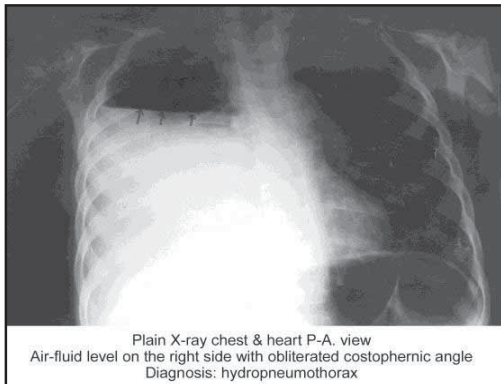
Clinical picture

Chest examination

- Inspection → Unilateral bulge.
- Palpation → Decreased TVF & trachea shifted to opposite side.
- Percussion → Shifting dullness.
- Auscultation → Marked diminished breath sounds.
→ Succession splash

Investigations

- As pleural effusion;
- Chest X-ray → air- fluid level



Treatment

- 1- Antibiotics according to culture and sensitivity.
- 2- Closed drainage with underwater seal⇒ If failed → surgical closure of the fistula.

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Pneumothorax

Definition: Presence of air in the pleural cavity

Causes

- Rupture pneumatocoles
- Rupture tuberculous cavity
- Rupture lung abscess.
- Rupture surface alveoli in air trapping
- Vigorous resuscitation
- Chest wall trauma

Clinical picture

Symptoms

- Asymptomatic (in small pneumothorax) → discovered accidentally
- Symptomatic: → Respiratory distress (↑↑ with tension pneumothorax).
→ Symptoms of the cause

Chest examination

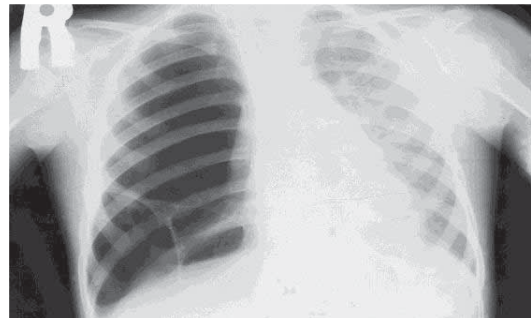
- Inspection → Unilateral decreased movement & unilateral bulge.
- Palpation → Decreased TVF & trachea shifted to opposite side.
- Percussion → Hyper resonance.
- Auscultation → Marked diminished breath sounds.
→ Coin test

Evidence of tension

- Mediastinal shift
- Circulatory compromise
- Hearing a "hiss" of rapid exit of air under tension with the insertion of the thoracostomy tube

Investigations

- Chest X-ray/CT → jet black opacity
± mediastinal shift to the opposite side
- CT chest: may identify underlying pathology such as blebs
- For the cause



Treatment

- 1- Small pneumothorax: usually resolve within 1 week.
- 2- Symptomatic:
 - Closed drainage with underwater seal.
 - Tube is inserted in the 2nd space mid clavicular line.
- 3- Treat the underlying cause.

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Tuberculosis

Definition

Chronic infectious disease caused by Mycobacterium TB bacilli (human and bovine types) which is alcohol and acid fast aerobic intracellular bacilli.

Modes of transmission

- Inhalation → pulmonary tuberculosis
- Ingestion(with milk) → intestinal T.B(& tonsillar tuberculosis)
- Wound contamination → cutaneous tuberculosis
- Hematological spread form primary T.B. focus

Risk factors

- Children exposed to high-risk adults
- Low Socioeconomic standard (Homeless persons)
- Suppressed immunity e.g. HIV, malnutrition & immunosuppressive therapy
- Susceptible age: disease is more severe in infants and young child
- Susceptible Race: More in Negroes

Pathogenesis

Primary exposure to T.B bacilli result in formation of primary complex at the site of entry of the bacilli (the commonest form in children).

1. Primary pulmonary complex:

- Composed of
- Primary focus (Ghon's focus)
 - Lymphangitis
 - Hilar lymphadenitis

2. Primary cervical complex (tonsillar T.B)

- Composed of
- Primary focus in tonsils
 - Lymphangitis
 - Cervical lymphadenitis

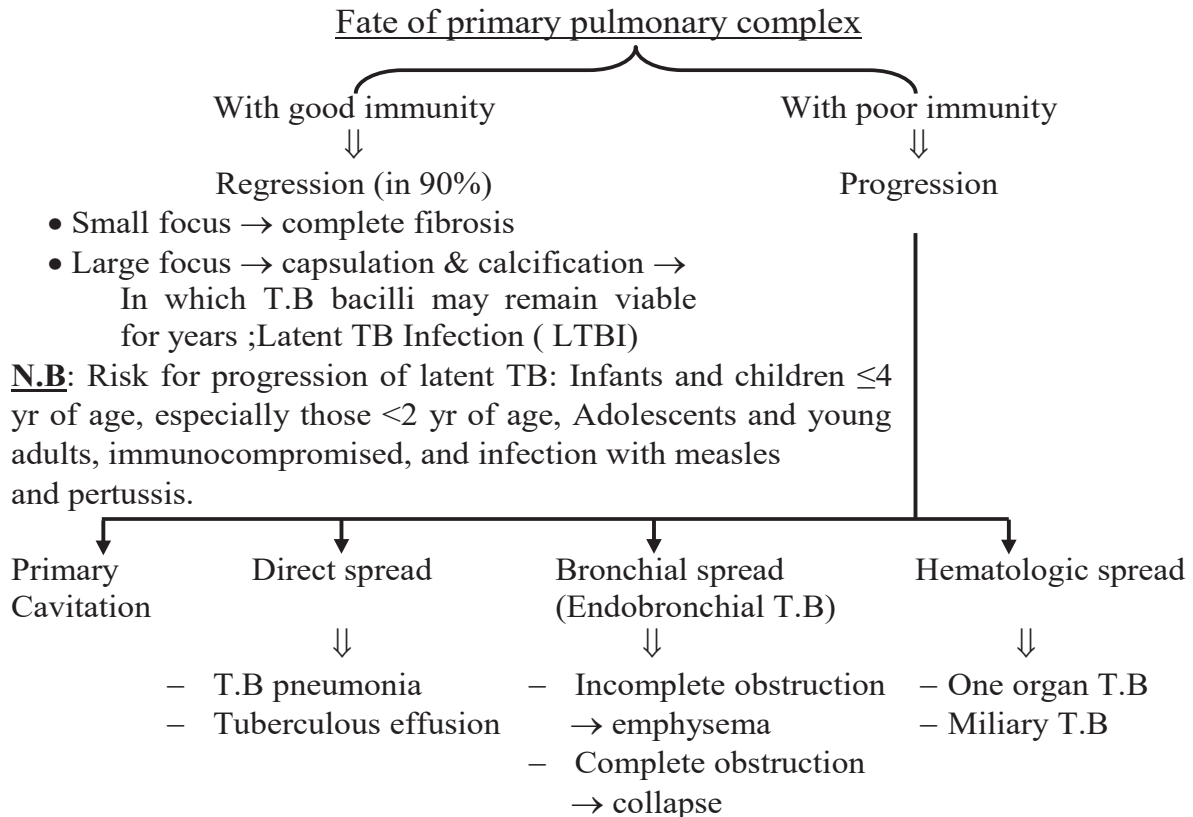
3. Primary intestinal complex

- Composed of
- Primary focus in pyere's patches
 - Lymphangitis
 - Mesenteric lymphadenitis

Each primary focus is formed of tubercles each tubercle is formed of :

- Central caseation
- Epitheloid cells
- Macrophages and lymphocytes
- Langerhans giant cells





Clinical stages of tuberculosis

There are 3 major clinical stages of tuberculosis

Exposure

- The child has had significant contact (“shared the air”) with an adult with infectious tuberculosis but lacks proof of infection : →Negative tuberculin skin test (TST) or interferon- γ release assay (IGRA)
- Normal physical examination
- Normal chest radiograph
- These cases have risk of developing tuberculosis disease rapidly

Infection

- The child inhales droplet nuclei containing *M. tuberculosis*, which survive intracellularly within the lung and associated lymphoid tissue
- Positive TST or IGRA are the hallmark of tuberculosis infection
- Normal physical examination
- The chest radiograph is either normal or reveals only granuloma or calcifications in the lung parenchyma.

Disease

Occurs when signs or symptoms or radiographic manifestations caused by *M. tuberculosis* become apparent

(Nelson textbook of pediatrics, 2016)

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Clinical Picture

1. Pulmonary TB

Common

- ✓ Asymptomatic in up to 50%; may be mild fatigue & poor appetite
- ✓ Nonproductive cough and mild dyspnea are the most common symptoms
- ✓ Some infants have difficulty gaining weight or frank failure-to-thrive

May be

- Hilar lymphadenopathy may present with:
 - Obstructive emphysema/wheezing: due to partial bronchial obstruction
 - Lung collapse: due to complete bronchial obstruction
 - Positive D'Espine sign (Bronchial breathing below level of tracheal bifurcation)
- Wheezy chest : due to endobronchial TB with partial bronchial obstruction
- Allergic manifestations:



- Erythema nodosum
- Phlyctenular keratoconjunctivitis
- Toxic manifestations (uncommon) → night fever & sweating.
- Manifestations of extension; usually with toxic manifestations and hectic fever e.g. Bronchopneumonia, tuberculous effusion, miliary tuberculosis

N.B. *Cough with sputum is rare, seen literally in progressive primary pulmonary TB with formation of T.B cavity.*

2. Extra pulmonary tuberculosis

A. Tuberculous lymphadenopathy

Common sites: Cervical, Mediastinal, Mesenteric

Criteria:

- Firm
- Non-tender
- Early discrete then matted after caseation

Complications:

- Cold abscess
- Draining sinus

Diagnosis: Biopsy and histologic examination



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B. Miliary tuberculosis

- Hematogenous spread of tubercle bacilli from any focus (usually pulmonary) → causing disease in 2 or more organs; lung, kidneys, liver, spleen, bone marrow, meninges.
- Usually complicates the primary infection, occurring within 2-6 mo of the initial infection

Common in

Infants, malnourished, immunosuppressed, with measles or pertussis

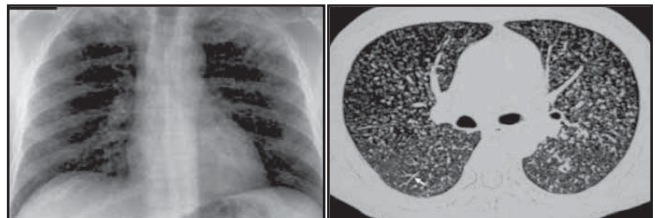
Clinical picture

- Often, the onset is insidious, with anorexia, weight loss, and low-grade fever
- Weeks later:
 - Generalized lymphadenopathy and hepatosplenomegaly
 - Fever higher and more sustained
- Weeks later:
 - The lungs become filled with tubercles → dyspnea, cough, rales, or wheezing. May be respiratory distress, hypoxia, and pneumothorax
 - Meningitis (recurrent headache) or peritonitis (abdominal pain) are found in 20-40%
 - Cutaneous lesions include papulonecrotic tuberculids, nodules, or purpura

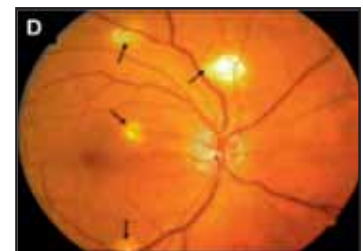


Diagnosis

1. **History** of recent exposure to an adult with infectious TB → The most important clue
2. **Biopsy** of the liver or bone marrow with appropriate bacteriologic and histologic examinations more often yields an *early diagnosis*
3. **Chest x ray/CT:**
 - Small miliary shadows; < 2-3 mm
(*Snow storm opacities*)



4. **Fundus examination:**
 - Show choroid tubercles in 13-87 %
 - Highly specific



5. TST is non-reactive in 40 %

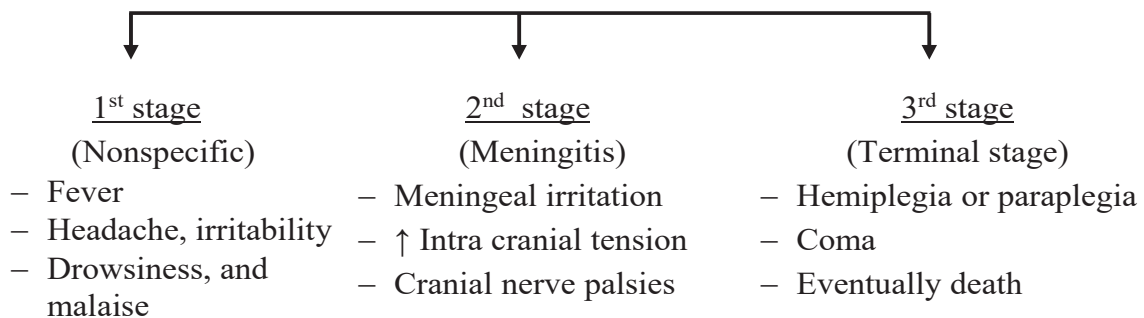
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C. Tuberculous meningitis

- Complicates about 0.3% of untreated tuberculosis infections in children
- Due to hematogenous spread either isolated or as a part of miliary TB
- Tubercle bacilli spreading into the subarachnoid space form a gelatinous exudate that infiltrates the corticomeningeal blood vessels, producing inflammation, obstruction, and subsequent infarction of cerebral cortex

Clinical picture

- In infancy and early childhood
- Insidious onset
- Pass in **3** stages (each lasts 1-2 weeks)



D. Intestinal tuberculosis

Occur secondary to

- Ingested tubercle bacilli in milk
- Swallowed sputum from tuberculous lesions in the lungs

Clinical picture

- Tabes mesenterica; enlarged mesenteric lymph nodes.
- Tuberculous enteritis:
 - Chronic diarrhea → failure to thrive
 - Chronic abdominal pain

E. Tuberculous peritonitis

Occur 2^{ry} to: Spread from intestinal or genitourinary T.B lesions

Clinical picture

- Ascites
- May be adhesions.

F. Pott's disease

Common sites: mainly affect lower dorsal spine.

Clinically

- Back pain and stiffness
- Cold abscess formation with persistent angular kyphosis

X ray spine: Diagnostic

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Diagnosis of tuberculosis

1. **History** of recent exposure to an adult with infectious TB → The most important clue

2. **Tuberculin Skin Test (TST):**

- Detects delayed hypersensitivity reaction to tuberculo-protein
- Mantoux test: intradermal injection of 0.1 ml containing 5 tuberculin units of purified protein derivative (PPD).
- Interpretation: measure the induration after **48 -72** hours
- Indications : see later

A. Positive test (= TB infection or disease)

1. Induration $\geq 5 \text{ mm}^2$ in high risk patients;
 - Close contact with active tuberculosis patient
 - Immunodeficiency
 - Child having clinical or chest x ray compatible with tuberculosis
2. Induration $\geq 10 \text{ mm}^2$ in moderate risk patients;
 - Child < 4 years
 - Child from endemic area or exposed to people from endemic area
 - Chronic diseases with increased risk e.g. diabetes , renal diseases
3. Induration $\geq 15 \text{ mm}^2$ in any child above 4 years without risk factors



B. False positive test; usually less than 10 mm induration, consider:

- Recent BCG vaccination; reactivity is lost by 5-10 years after vaccine
- Non tuberculous mycobacteria

C. Negative test: induration less than 5 mm²

- True negative test → no T.B infection
- False negative test → in
 - Technical error
 - Transient suppression of tuberculin reactivity with viral infections e.g. measles, mumps or live virus immunization
 - Early in the disease
 - Miliary TB.
 - Immunodeficiency

3. **Interferon- γ Release Assays (IGRA)**

- Two blood tests available (T-SPOT.TB and QuantiFERON-TB)
- Detect IFN- γ generation by the patient's T cells in response to specific human *M. tuberculosis* antigens
- Like the TST, IGRAs cannot differentiate between tuberculosis infection and disease.

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Advantages

- Lack of cross-reaction with BCG vaccination and most other mycobacteria
- One spot test; unlike TST

Indications:

- CDC recommends using IGRA interchangeably with TST

Indications of TST or IGRA

1. Contacts of people with confirmed or suspected contagious TB
2. Children with radiographic or clinical findings suggesting tuberculosis
3. Children immigrating from countries with endemic infection (e.g. Asia, Middle East)
4. Children with travel histories to countries with endemic infection
5. Children infected with HIV should have annual TST or IGRA
6. Before initiation of immunosuppressive therapy e.g. Prolonged steroid

- Specific indications of IGRA:

- Child ≥ 5 yr who have a positive TST and have received the BCG vaccine
- If nontuberculous mycobacterial disease is suspected
- Child ≥ 5 yr who is unlikely to return for TST reading
- Supportive to positive TST before starting therapy

(Nelson textbook of pediatrics, 2016)

4. Specific:**A. Pulmonary tuberculosis**

1. Isolate *M. tuberculosis*:

Sampling

- Expecterated sputum in older children
- Induced sputum with a jet nebulizer and chest percussion followed by nasopharyngeal suctioning is effective in children as young as 1 year
- 3 consecutive early morning gastric aspirate before the infant has arisen

Workup

- Acid-fast bacilli staining (Zehl Nelsen stain and light microscopy)
- Culture
- Polymerase chain reaction ;PCR(of limited value)
- Recently , Gene Xpert MTB/RIF is a real-time PCR assay for *M. tuberculosis* that simultaneously detects rifampin resistance

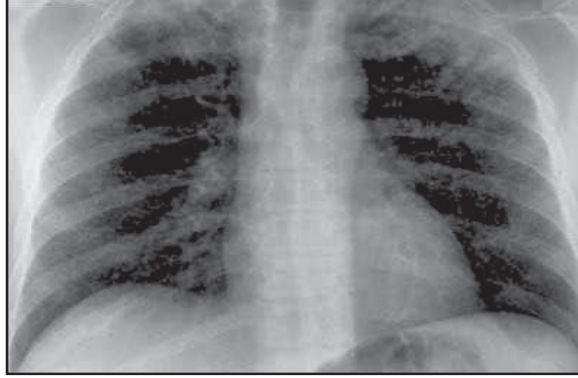
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N.B For many forms of tuberculosis, the culture yield is only 25-50%. So, negative cultures never exclude the diagnosis of tuberculosis in a child.

2. Chest X-ray: May reveal



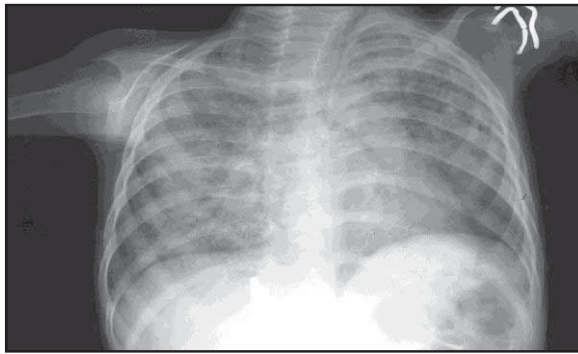
Enlarged hilar lymph nodes
Localized emphysema



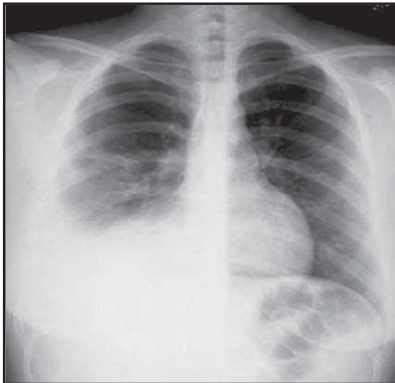
Miliary TB; small miliary shadows 1-2 mm (snowflake opacities).



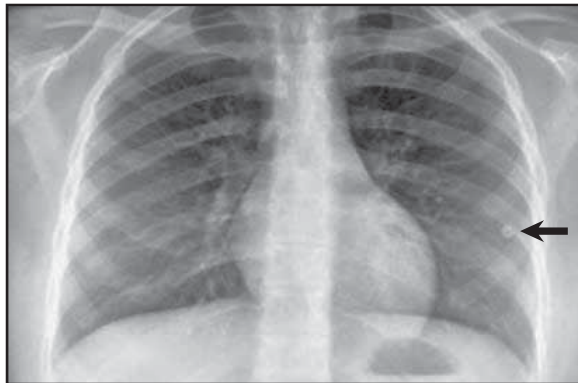
Enlarged hilar lymph nodes
Localized collapse



T.B bronchopneumonia ;fluffy cotton appearance



Pleural effusion



Calcified granuloma (primary focus)

3. Detect the pathology:

- Pleural biopsy
- Lymph nodes biopsy
- Bronchoscopy (for suspected endobronchial TB) and biopsy



4. Pleural fluid examination:

- Color : Yellow with blood tinge
- Characters: Usually unilateral, massive; recollect after aspiration
- Cells : ↑ lymphocytes but it is very rare to discover T.B bacilli
- Cultures of the fluid are positive in <30% of cases.

5. Blood: Elevated ESR

B. Tuberculous meningitis

- Lumbar puncture and CSF analysis, culture and PCR(See neurology)
- CT, MRI may detect *tuberculoma*; a tumor-like mass resulting from aggregation of caseous tubercles



MRI of brain of a 3 yr old child showing multiple pontine tuberculomas
(Nelson 2016)

N.B The TST is nonreactive in up to 50% of cases, and 20-50% of children have a normal chest radiograph.

C. Intestinal tuberculosis:

- Mesentric lymph node biopsy
- Ascitic fluid analysis

The presence of a positive TST or IGRA, an abnormal chest radiograph consistent with tuberculosis, and history of exposure to an adult with infectious tuberculosis is adequate for the probable diagnosis of tuberculosis disease

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Treatment

Prevention

- * BCG vaccine (see before)
- * Milk sanitation (boil milk for 10- 15 minutes before use)
- * Isolate and treat infective cases with open pulmonary TB.
- * Avoid contact with cases.
- * **Window prophylaxis:**
 - For children who:
 - Have unavoidable close contact to an adult with potentially contagious tuberculosis disease and
 - Have a negative TST or IGRA result
 - Break the contact with the source case for tuberculosis (i.e. physical separation or adequate initial treatment of the source case) and Give INH 10 mg/kg/d for **3** months (the time delayed hypersensitivity develops)
 - Perform TST or IGRA at **3** months
 - If positive result ($\geq 5 \text{ mm}^2$) → continue INH for **9** months
 - If negative result → stop INH and INH resistant BCG can be given
 - Trace the possible adult source and treat adequately to prevent other secondary cases.

Curative

A. General lines

- Good nutrition, fresh air
- Follow up carefully to promote adherence to therapy, and to monitor for toxic reactions to medications

B. Anti-Tuberculous drugs

First line drugs

Drug	Daily dose*	Twice weekly dose *	Side effects
▪ Isoniazide (INH)	10-15	Double the dose	- Hepatotoxic - Peripheral neuritis (?? add vit B ₆)
▪ Rifampicin	10-20	Same	- Hepatotoxic - Red staining of secretions
▪ Pyrazinamide	20-40	50	- Hepatotoxic - Hyperuricaemia
▪ Ethambutol	20	50	- Optic neuritis (usually reversible) - Color blindness (green, red)

* mg/kg

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Alternative drugs

Used as additive drugs in

- Multiple drug resistant tuberculosis
- Life threatening tuberculosis e.g. T.B. meningitis.

Drug	Dose (mg/kg/d)	Side effects
▪ Streptomycin	20-40 (I.M)	Ototoxic & nephrotoxic
▪ Ethionamide	15-20 (oral)	Hepatotoxic (similar to INH).
▪ Amikacin	15-30 (IM)	As streptomycin

Regimens for treatment

The specific treatment plan must be individualized for each patient according to the results of susceptibility testing on the isolates from the child or the adult source case

1. Six months regimen

- Standard therapy for intrathoracic tuberculosis and cervical lymphadenopathy
- Rifampicin and INH (for 6 months) + Pyrazinamide and Ethambutol (in the 1st 2 months)

1. Rifampicin
2. INH
3. Pyrazinamide
4. Ethambutol
For 2 months

Rifampicin + INH
For 4 months

- When **directly observed therapy** is used: initial period as short as 2 wk of daily therapy followed by intermittent (twice weekly) therapy is as effective as daily therapy for the entire course.

2. Nine month regimen

- Using only isoniazid and rifampin
- Highly effective for drug-susceptible tuberculosis
- Carry risk of initial drug resistance and poor compliance

3. In miliary T.B, meningitis and bone T.B

- Extend treatment period for 9-12 months.

4. In drug resistance

- Treatment is undertaken by a clinician with specific expertise
- Initial treatment
 - Isoniazid resistance ⇒ 9 mo with rifampin, pyrazinamide, and ethambutol
 - Isoniazid and rifampin resistance ⇒ extend total duration of therapy to 12-24mo, and avoid twice-a-week regimens

5. Latent TB infection: isoniazid for 6-9 months

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Steroids in T.B

Used in

- 1- Miliary tuberculosis → to improve the general condition
- 2- Endobronchial tuberculosis with localized emphysema.
- 3- Enlarged hilar lymph nodes with airway obstruction.
- 4- Tuberculosis of serous cavities e.g Pleurisy , Pericarditis , Meningitis
- 5- Adrenal tuberculosis

Precautions

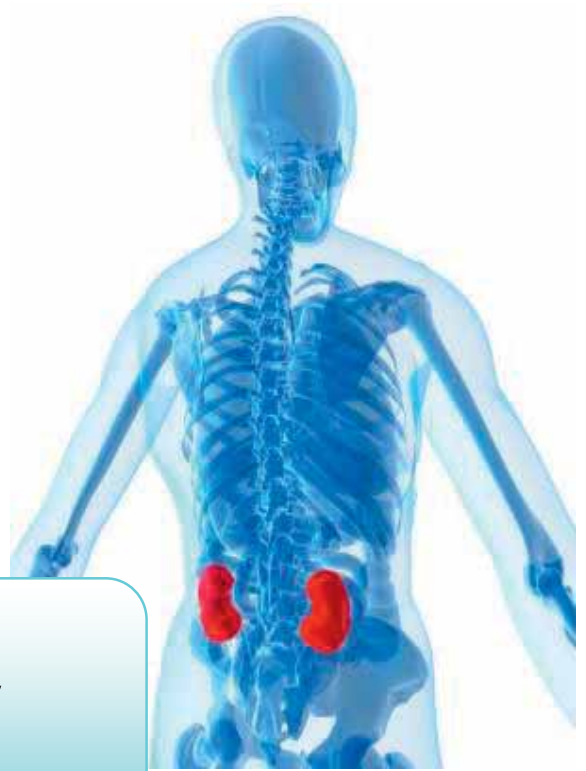
- 1- Under umbrella of antituberculous drugs.
- 2- Dose 2 mg/kg/d for 4-6 weeks followed by gradual tapering.

Respiratory failure

Definition: Failure of the lungs to keep normal level of arterial blood gases(O₂ & CO₂)

	Peripheral(type I)	Central (type II)
Causes	<ul style="list-style-type: none"> - Airway obstruction e.g asthma - Pneumonia - Pneumothorax - Massive effusion 	<ul style="list-style-type: none"> - Brain : hemorrhage, drugs - Neuromuscular: spinal muscle atrophy, Guillian Barre syndrome - Skeletal: severe kyphosis, scoliosis
Clinically	<ul style="list-style-type: none"> * Manifestations of the cause * Respiratory distress * Mainly hypoxemia: irritability, restless, dizziness , cold pale extremities 	<ul style="list-style-type: none"> * Manifestations of the cause * Irregular , shallow respiration * Mainly hypercapnia: cyanosis, lethargy, headache and impaired consciousness
ABGs	↓PaO ₂ – ↑PaCO ₂ – ↓pH	
Treatment	Treat the cause Oxygen therapy(See neonates)	Treat the cause Ventilation

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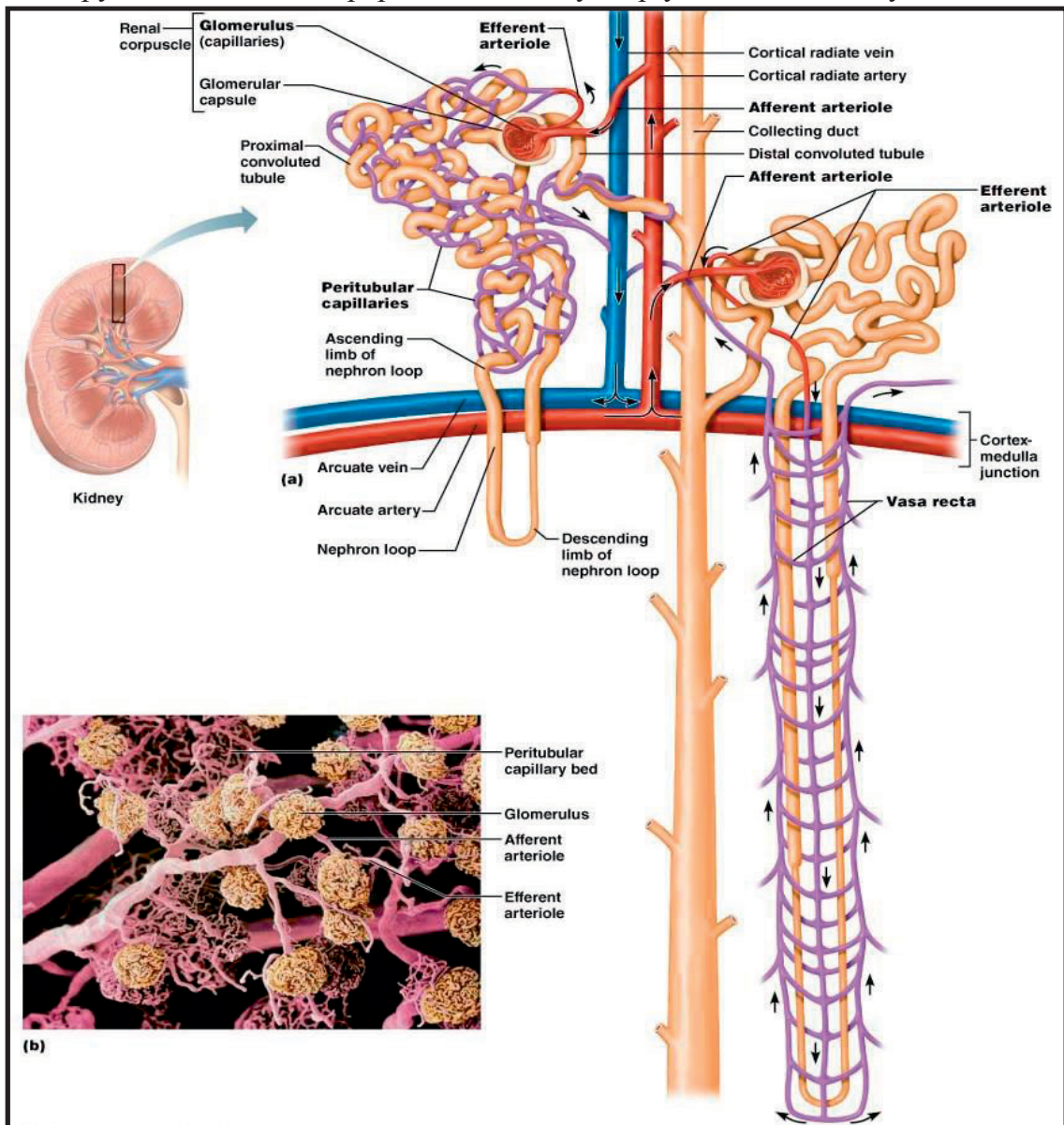
Nephrology

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الدفعة الـ 14

Structure of the Nephron

- Nephrons are the structural and functional units of the kidneys that carry out processes that form urine
- Each nephron consists of a renal corpuscle composed of a tuft of capillaries (the glomerulus), surrounded by a glomerular capsule (Bowman's capsule) and a renal tubule. The renal tubule begins at the glomerular capsule as the proximal convoluted tubule, the loop of Henle, and turns into a distal convoluted tubule before emptying into a collecting duct.
- The collecting ducts collect filtrate from many nephrons, and extend through the renal pyramid to the renal papilla, where they empty into a minor calyx



Note: - Efferent arterioles provide blood supply to the whole renal tubules
 - Erythropoietin is produced by peritubular capillary endothelium cells

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Functions of the Nephron

Glomerular filtration:

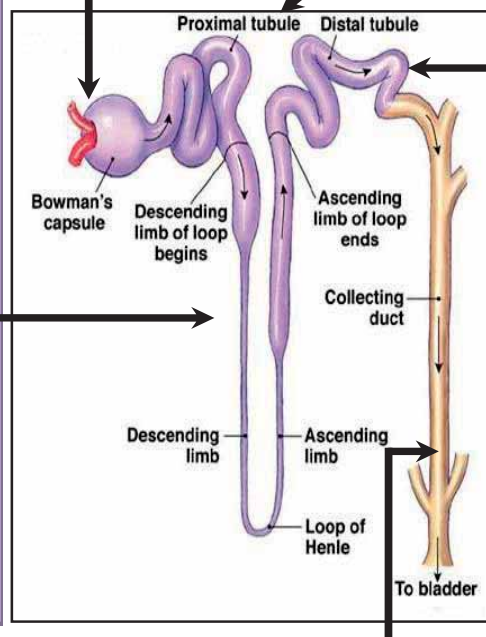
- Plasma is passively **filtered** through the glomerular capillary walls.
- The ultrafiltrate, which is cell free, contains all of the substances in plasma (water, electrolytes, glucose, phosphate, urea, creatinine, peptides, low molecular weight proteins) except proteins having a molecular weight of ≥ 68 kd (e.g. albumin and globulins).

Reabsorption at the PCT (Main bulk)

- Sodium: 65-70% of filtered by active transport by Na-K pump
- Water :By osmosis (65-70% of filtered water) as obligatory water reabsorption
- HCO₃: Linked to sodium transport
- Nutrients :100% of glucose, amino acids, vitamins by secondary active transport
- Phosphate (80% reabsorbed)
- Ions: Ca, Mg, K by passive diffusion

Loop of Henle:

- Na, K, Cl: active transport by Na-K-2Cl cotransporter in ascending limb (These transporters are the targets for loop diuretics e.g. **Furosemide**)
- Water :By osmosis (10% of filtered water) in descending limb helped by ADH



Distal tubules : (DT)

- Early DT has Na⁺-Cl⁻ cotransporters (inhibited by **Thiazide** diuretics)
- Late DT has Na⁺ (and K⁺) channels that are increased by aldosterone hormone (inhibited by K sparing diuretics e.g. **Amelioride**). Net result is Na reabsorption and secretion of either K⁺ or H⁺ and
- Water reabsorption follows Na
- Reabsorption of Ca controlled by parathyroid hormone

Collecting ducts:

- Like late DT, the collecting tubule has Na⁺ (and K⁺) channels induced by Aldosterone
- Water reabsorption secondary to Na reabsorption and passive osmosis 2ry to interstitial hypertonicity with help of Antidiuretic hormone

Summary of renal functions:

- Control body water**
- Get rid of waste e.g. Blood urea nitrogen , creatinine, H⁺, excess K⁺, Drugs**
- Regulation of acid –base balance by:**
 - About 90% of filtered bicarbonate is absorbed in the **proximal tubule** aided by carbonic anhydrase (CA)
 - Secretion of hydrogen ion as titratable acid or as NH₄⁺ at the **distal tubule**
- Hormonal role e.g. Release of Erythropoietin, Activation of vit D**

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Estimation of Glomerular Filtration Rate (GFR)

- Formation of nephrons is complete at 36-40 wk of gestation, but functional maturation with tubular growth and elongation continues during the 1st decade of life
- Because new nephrons cannot be formed after birth, any disease that results in progressive loss of nephrons can lead to renal insufficiency

Serum creatinine:

- Estimates the GFR in the steady state
- Insensitive measure of decreased renal function because its level does not rise above normal until the GFR falls by 30-40%

Clearance tests (require timed urine collection)

- The clearance is represented by the following formula:

$$C_s (\text{mL min}) = U_s (\text{mg mL}) \times V (\text{mL min}) / P_s (\text{mg mL})$$
 Where C_s equals the clearance of substance s , U_s reflects the urinary concentration of s , V represents the urinary flow rate, and P_s equals the plasma concentration of s .
- To correct the clearance for body surface area, the formula is

$$\text{Corrected clearance (mL/ min/1.73m}^2) = C (\text{ml/min}) \times 1.73 / \text{Surface area (m}^2)$$
- Clearance substances
 - Exogenous: Inulin clearance (Gold standard – Difficult)
 - Endogenous: Creatinine clearance

Formula in pediatrics:

1. Haycock-Schwartz formula

$$e\text{GFR} = k \times ht / P_{\text{cr}}$$

eGFR	Estimated glomerular filtration rate(in ml/min/1.73m ²)
k	Empirical value relating height to muscle mass = 0.33 for LBW infant = 0.45 for Full term infant = 0.55 for child or adolescent girl = 0.7 for adolescent boy (13-18 years old)
ht	Height in centimeters
P _{cr}	Plasma concentration of creatinine in mg/dl

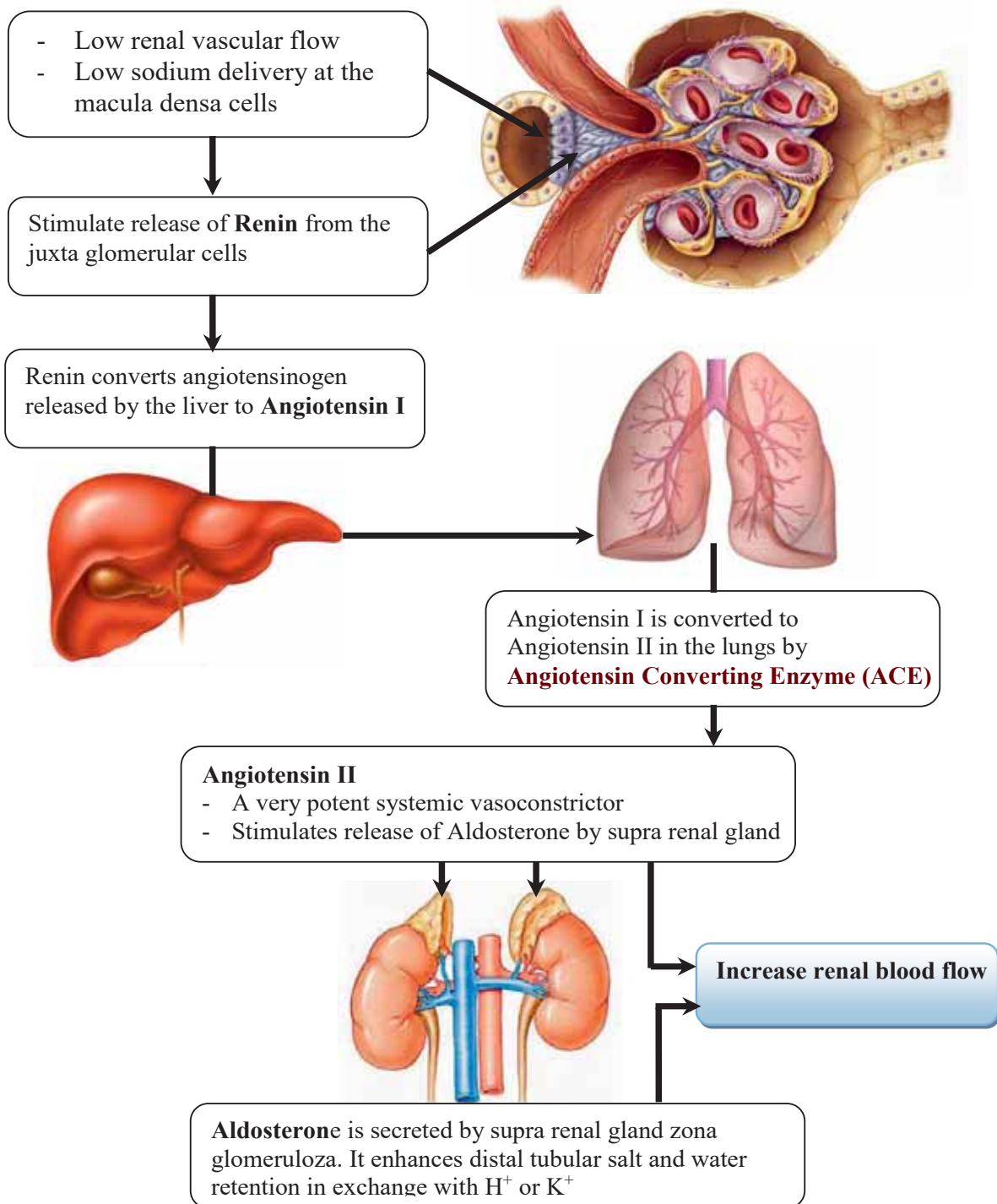
When timed urine collection is not possible, simply Haycock-Schwartz formula is the best, easiest and cheapest way to assess GFR.

2. DTPA scan: Can assess split functions of both kidneys

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Control of renal hemodynamics occurs through the following mechanisms:

1. Renin-Angiotensin-Aldosterone System (RAAS) primed by Juxtaglomerular apparatus (JGA): composed of two cell types, macula densa cells(modified distal tubular cells) and juxtaglomerular cells, located at the junction of the afferent and efferent arterioles



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2. Intra renal prostaglandins

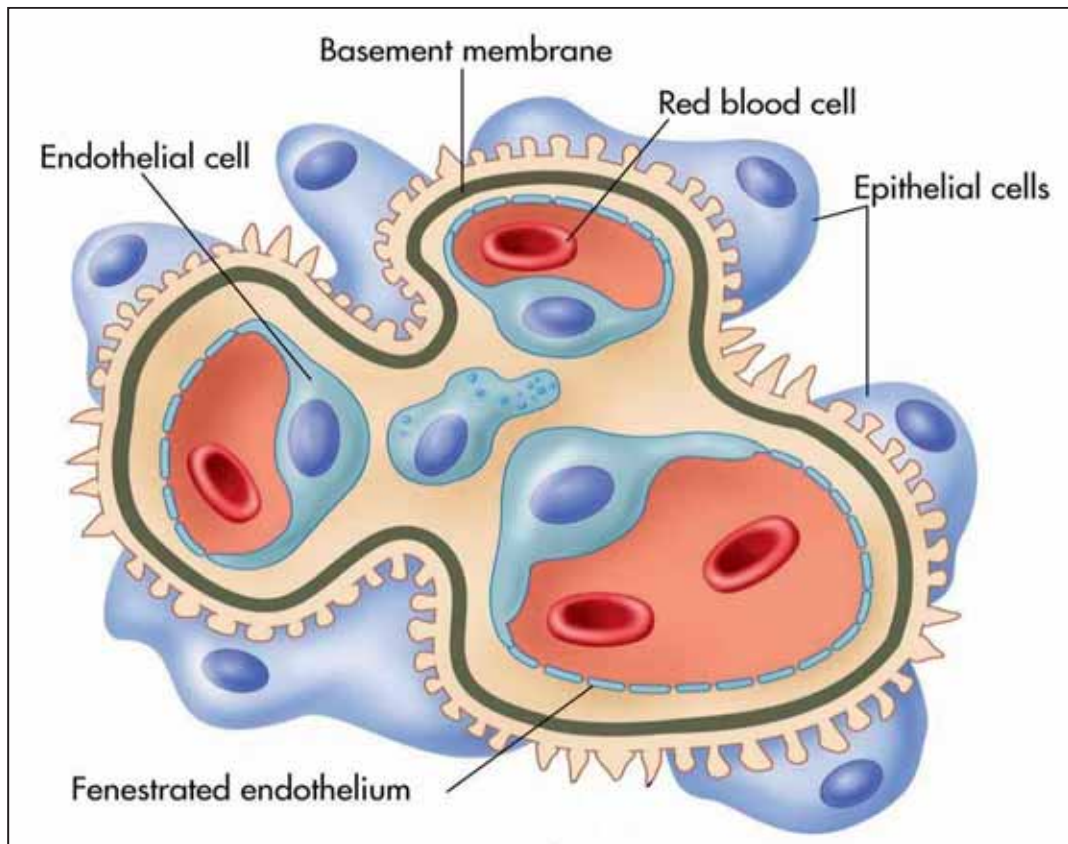
- PGE2 and prostacyclin [PGI2] are vasodilators
- They counteract primarily angiotensin II-mediated vasoconstriction
- Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin will block prostaglandin synthesis and restrict the compensatory renal vasodilation

3. Atrial natriuretic peptide (ANP)

- Is released from the right cardiac atrial myocytes in response to stretch (at high blood volume)
- ANP dilates the afferent arteriole, and constricts the efferent arteriole, increasing glomerular capillaries hydrostatic pressure, and thus, GFR.
- The enhanced flow increases sodium and water excretion, reducing blood volume.

Blood filtrate barrier ultrastructure

1. Epithelial cells (Podocytes)
2. Glomerular basement membrane
3. Endothelial cells



Hematuria

Definition

- **Macroscopic (Gross) hematuria:** Blood in the urine visible to the naked eye
- **Microscopic hematuria:**
 - More than **5** red blood cells (RBCs) per high-power field on freshly voided and centrifuged urine
 - Isolated asymptomatic microscopic hematuria is found in up to 4% of healthy children.

Presentation

- Episode of macroscopic hematuria (causes alarm to child/family).
- Incidental finding of microscopic hematuria.
- Family screening and routine urinalysis.

Other causes of 'red urine'

The following can usually be distinguished from hematuria by taking a careful history, and with urine dipstick testing and microscopy:

- A. Pathologic
 - Hemoglobinuria
 - Myoglobinuria
- B. Non pathologic
 - Foods coloring (e.g. beetroot).
 - Drugs (e.g. rifampicin).
 - Urate crystals (in young infants, usually 'pink' nappies).
 - External source (e.g. menstrual blood losses).
 - Fictitious: consider if no cause found

Causes of haematuria

A. Glomerular

1. Immunologic injury :Glomerulonephritis (GN)
2. Structural disorder (Alport syndrome, thin basement membrane disease)
3. Toxin-mediated injury (HUS)

B. Extra Glomerular

- **Tubulo interstitial/Parenchymal**
 - a. Inflammation (interstitial nephritis, pyelonephritis)
 - b. Vascular (sickle cell trait/disease, renal vein thrombosis)
 - c. Structural (cyst rupture, Wilms tumor, urinary tract obstruction, trauma)
- **Lower urinary tract**
 - a. Inflammation (cystitis, hemorrhagic cystitis, urethritis)
 - b. Injury (trauma, kidney stone)
 - c. Hypercalciuria

(Essential Nelson)

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Glomerulonephritis (GN)

Definition: Group of diseases with acute glomerular injury. Initiated in most cases by immunologic mechanism. With variable presentation of:

- Acute kidney injury (AKI) (oliguria, uremia, elevated creatinine)
- Hematuria
- Hypertension
- Peripheral edema
- Proteinuria

Classification

With low serum complement (C3,CH50)	With normal serum complement
Renal disease	Renal disease
<ul style="list-style-type: none"> ▪ Acute post infectious GN (> 90%) <ul style="list-style-type: none"> - Post streptococcal GN - Other infections: e.g. staph, pneumococci, HBV, ▪ Membranoproliferative GN type 1 	<ul style="list-style-type: none"> ▪ IgA nephropathy
Systemic disease	Systemic disease
<ul style="list-style-type: none"> ▪ Chronic Post infectious GN: <ul style="list-style-type: none"> - Infected shunt - Infective endocarditis ▪ Lupus nephritis 	<ul style="list-style-type: none"> ▪ Vasculitis ▪ Henoch-Schönlein purpura ▪ Goodpasture's syndrome

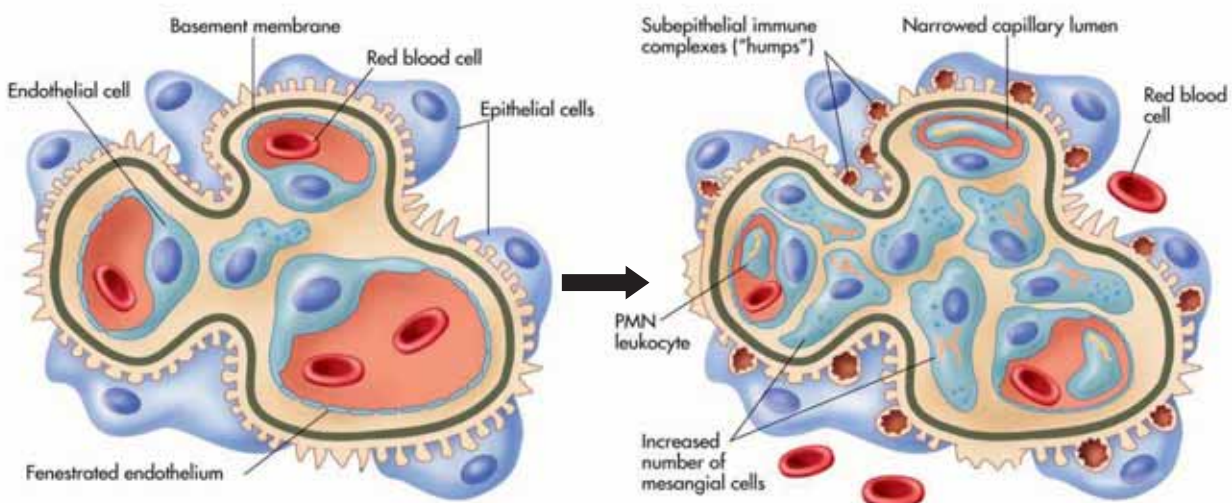
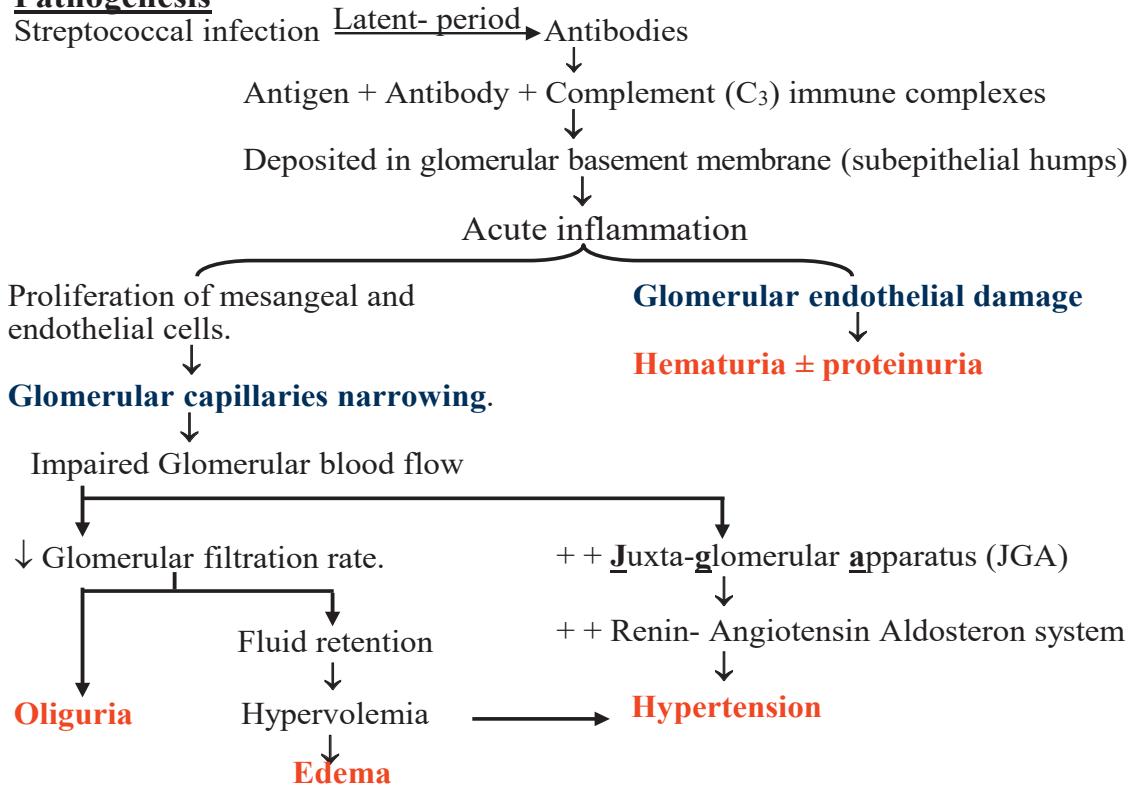
Acute Post Streptococcal Glomerulonephritis (APSGN)

Definition and Etiology

- Acute Nephritic syndrome which follow infection with nephritogenic strain of group A- β hemolytic streptococci causing throat infection or skin infection
- Streptococcal pyogenic exotoxin (SPEB) mimic glomerular basement membrane

	Post pharyngitis GN	Post skin infection GN
Stains of strept.	- Serotypes :1,3, 4,12,18	- Serotypes :2,49,55,57
Season	- Cold(winter)	- Tropical(summer)
Sex incidence (M: F ratio)	- 2:1	- 1:1
Susceptible age	- School age	- Pre School age
Latent period	- 1-2 weeks	- 2-6 weeks; typically in child with eczema
Serology:		
ASO titer	- Elevated	- May be absent
Anti DNase B	- Elevated	- Elevated

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Pathogenesis

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Clinical picture

Mean age: 7 years.

History of a preceding skin or throat infection 1-3 weeks ago may be obtained

Gradual or sudden onset of:

- 1. Hematuria** : - The 1st presenting feature
 - Painless
 - Cola colored (smoky) urine or bloody with gross hematuria
 - Urine rarely appears normal with microscopic hematuria



- 2. Edema** : - 2nd presenting feature
 - Mild, morning periorbital puffiness & pretibial edema
 - Mainly due to reduced GFR and hypervolemia
- 3. Oliguria** : - Urine output (UOP) < 1 ml/kg/hr or < 400 ml/m²/day
 - Some others have anuria or rarely normal urine volume
- 4. Hypertension** : - Transient ; mostly resolves by the end of 1st week
 - Mild to severe
 - Seen in 60-70% at any time in the acute phase
 - Principally due to *salt and water retention*

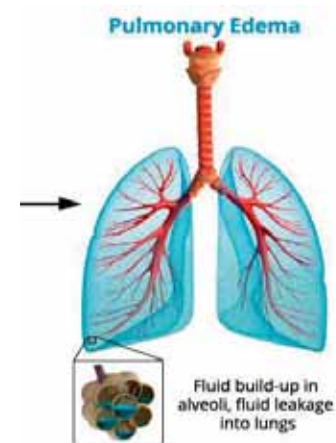
5. Nonspecific: - Headache, anorexia, vomiting, abdominal pain, mild fever.

6. Some cases are asymptomatic and discovered accidentally on routine urinalysis

Complications: May be the presenting event

1. Heart Failure and acute pulmonary edema

- Due to hypertension or hypervolemia
- Clinically
 - Respiratory distress and orthopnea
 - Tachycardia, tachypnea, tender liver
 - Acute pulmonary edema
 - Severe respiratory distress
 - Cyanosis
 - Wide spread crepitations



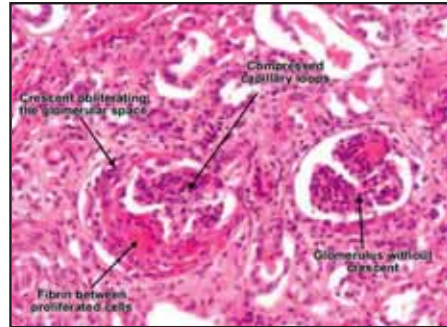
2. Hypertensive encephalopathy

- Due to acute hypertension → cerebral edema ± hemorrhages
- Clinically
 - Severe headache
 - Blurred vision
 - Vomiting → convulsions → coma

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3. **Acute renal failure (ARF)**

- Due to rapidly progressive (*crescentic*) GN
- Usually transient
- Clinically
 - Marked oliguria or anuria
 - Acidotic breathing
 - Uremic encephalopathy



Investigations

A. For diagnosis → Urinalysis

- Color: Smoky **or** gross hematuria.
- Specific gravity: High
- Proteinuria: Usually < 1gm/dl (nephrotic range is seen in 10-20%)
- Microscopy: Dysmorphic RBCs / RBCs casts which is pathognomonic to glomerular bleeding
- *Timed urine output collection or 24 hours collection can prove oliguria/anuria*

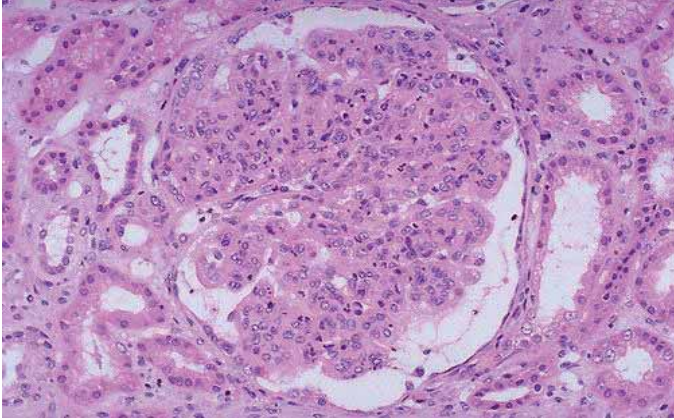
B. For effect

- Electrolytes → may be hyperkalemia & dilutional hyponatremia
- Renal function tests → may be impaired.
- Anemia → due to hemodilution

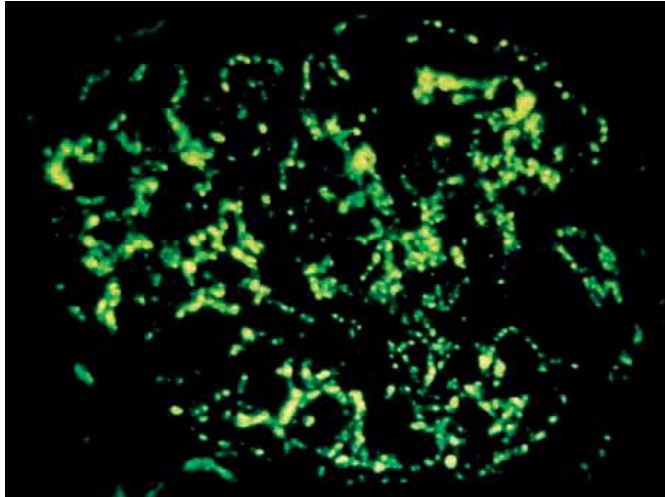
C. For etiology

- Low complement component C3 (Normal C4)
- Evidence of recent streptococcal infection:-
 - Throat or skin lesion swab culture
 - Anti- streptolysin O (ASO) titer → > 1/200 todd unit; may be negative after skin infection. (*ASO titer is raised in up to 20% of healthy children*)
 - Anti Deoxyribonuclease B titre (Anti- DNase B).
- **Renal biopsy** is indicated for :
 - a. In acute phase:**
 - Nephrotic syndrome (nephritic nephrosis)
 - Rapidly rising creatinine suggesting rapidly progressive glomerulonephritis
 - b. For prognosis in atypical course**
 - Abnormal creatinine at 6 weeks
 - Low C3 > 3 months
 - Proteinuria > 6 months

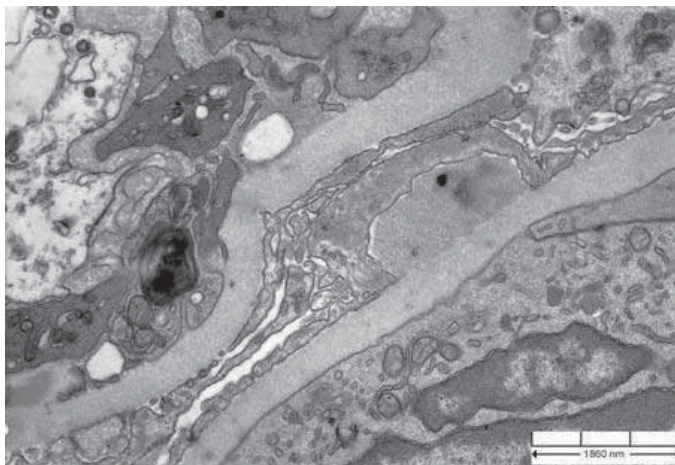
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Light microscopy**Glomerulus is**

- Hypercellular
- Capillary loops are poorly defined.
- Massive influx of neutrophils

Immunofluorescence microscopy**Reveals:**

"lumpy-bumpy" deposits of immunoglobulin and complement on the glomerular basement membrane (GBM) and in the mesangium

Electron microscopy**Reveals:**

Glomerular subepithelial cone-shaped electron-dense deposits, referred to as *"humps."*

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Course

- Nephritis manifestations usually resolve by 2-3 weeks
- C3 normalize by 6-8 weeks of onset
- Abnormal urinalysis improve within 4-8 weeks of onset
- Microscopic hematuria may persist for 1-2 years with *no long term relevance*

Differential diagnosis:

From other causes of Hematuria (see later)

Treatment

1. **B**ed rest as needed by the patient or with complications
2. **C**ourse of penicillin for 10 days is necessary to prevent spread to contacts but will not help the nephritis.
3. **D**iet
 - Assess fluid balance
 - Fluid restriction:
 - In oligo-anuria to avoid hypervolemia.
 - Intake = urine output plus insensible loss (200-400ml/m²/d or 20-40 ml/kg/day) plus any additional losses (vomitus or diarrhea)
 - Given as 0.45% saline /2.5 % dextrose or 0.45% saline /5-10 % dextrose in infants
 - Salt restriction
 - Potassium and protein restriction→ only with renal failure
 - Provide calories (reduce catabolism) by giving enteral *Maxijul* 10-20% via naso-gastric tube
4. Hypertension (**E**levated blood pressure):

<u>Mild to moderate hypertension</u>	<u>Severe hypertension</u>
<ul style="list-style-type: none"> - Fluid restriction - Furosemide 2-5 mg/kg IV - ACE inhibitor e.g Captopril - Angiotensin Receptor Blockers - Nifedipine or Amlodipine. 	<ul style="list-style-type: none"> - Furosemide - Na nitroprusside (infusion) - Hydralazine - Diazoxide (i.v. push).

5. Treat Complications (**F**ailures):

- ✧ Heart failure: Treatment depends on the underlying cause:
 - Hypertensive heart failure→ treat hypertension
 - Hypervolemic heart failure → diuretics ± dialysis.
- ✧ Acute renal failure:
 - Conservative treatment with or without peritoneal dialysis(see later)
 - Crescentic nephritis on biopsy may benefit from immunosuppression e.g. pulsed IV methylprednisolone

(Oxford Pediatric Nephrology)

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6. Discharge from hospital (Go home) if there is:

- No gross hematuria
- Normal renal functions
- No or controlled hypertension

Prognosis

- Over 95% of post streptococcal glomerulonephritis recover completely
- Less than 5% go into rapidly progressive glomerulonephritis may end in chronic renal failure.
- Mortality is due to heart failure, hypertension and renal failure
- Recurrence is extremely rare

IgA Nephropathy (Berger Nephropathy)

- IgA nephropathy is an immune complex disease
- It is characterized by a predominance of IgA within mesangial deposits of the glomerulus in the absence of systemic diseases such as systemic lupus erythematosus or Henoch-Schönlein purpura.
- The most common chronic glomerular disease worldwide.

Clinical

- Recurrent gross (macroscopic)hematuria*
 - Commonest presentation
 - Occur 1-2 days following upper respiratory tract infection
- Asymptomatic microscopic hematuria \pm proteinuria.
- Nephritic syndrome
- Nephrotic syndrome
- Nephritic-nephrotic syndrome.
- Progressive renal dysfunction in adulthood.

Diagnosis

- Normal serum levels of C3
- Serum IgA levels have *no diagnostic* value
- Renal biopsy : mesangial deposits of IgA

Treatment

There is no accepted treatment regimen; most are controversial.

A. Microscopic hematuria /recurrent gross hematuria:

- Of no clinical significance
- Tonsillectomy is advised by some investigators
- Some reports suggest vit E

B. Proteinuria & hypertension

- ACE inhibitors & angiotensin II receptor antagonists

C. Patients with adverse risk factors:

- Treat proteinuria and hypertension
- Immunosuppression including: steroids azathioprine, cyclophosphamide, mycophenolate mofetil (MMF)
- Fish oil (contains anti-inflammatory omega-3 fatty acids)
 - May decrease the rate of renal progression in patients with progressive disease
 - Preparation : Omacor capsule and Maxepa syrup
 - Main side effect is halitosis and none adherence

D. Successful renal transplantation

Recur in only 15–30% of patients

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Rapidly Progressive (Crescentic) Glomerulonephritis

Crescents in the majority of glomeruli progress rapidly to end-stage renal failure.

Causes

1- Immune complex glomerulonephritis:

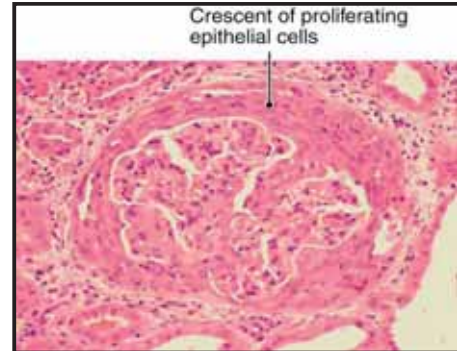
- Post-streptococcal glomerulonephritis.
- Henoch Shönlein purpura
- IgA nephropathy
- Lupus nephritis
- Membranoproliferative GN (MPGN)

2- Anti Glomerular Basement Membrane GN (Good Pasture Syndrome):

- Pulmonary hemorrhage and glomerulonephritis associated with antibodies against lung and against glomerular basement membrane (anti-GBM)
- Hemoptysis: is usually the presenting complaint (that may lead to death).
- Hematuria, proteinuria, and progressive renal failure
- Anti-GBM antibodies confirm the diagnosis

3- Idiopathic.

4- ANCA mediated glomerulonephritis (Wegner granulomatosis)



Pathology

- Characteristic Crescents inside Bowman capsule composed of:
 - Proliferating epithelial cells
 - Fibrin
 - Basement membrane like material
- Idiopathic form: absent deposits; only crescents.

Clinical picture:

Suspected in acute nephritic episode leading to acute renal failure

Diagnosis

- 1- Serologic studies e.g. C3, anti-Dnase-B,....
- 2- Renal biopsy

Prognosis and Treatment

- ☆ Spontaneous recovery may occur with post streptococcal type
- ☆ Treatment options (choice is cause related):
 - Pulsed methyle prednisolone / oral prednisone
 - Plasma exchange
 - Cyclophosphamide
 - Biological agents: Rituximab, Anti-TNF therapy
 - Supportive care of ARF e.g. Dialysis

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Hemolytic Uremic Syndrome (HUS)

Definition

- One of the most common causes of community-acquired acute kidney failure in young children
- It is characterized by the triad of : Microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency

Causes

1. Infection induced

- Often preceded by acute bloody diarrhea (*Typical HUS*) caused by:
 - Vero toxin -producing *E. coli* (Enterohemorrhagic *E. coli*); mainly O157:H7 (Europe , America)
 - Shiga toxin producing *Shigella dysenteriae type 1* (Asia-Africa)
 - ✓ Transmitted by undercooked meat or unpasteurized milk
 - ✓ Epidemics have followed ingestion of undercooked, contaminated hamburger at fast food restaurants
- Neuraminidase (T antigen) -producing *Strept.pneumonia* is a rare cause.

2. Other less common causes

Genetic (inherited HUS)

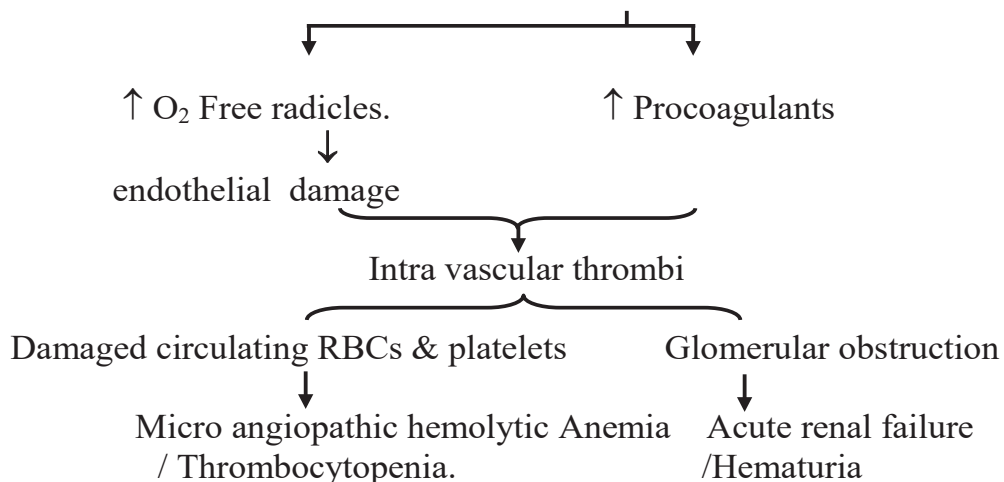
- Defective Von Willebrand factor–cleaving protease (ADAMTS 13)
- Defective Complement factor H, I, or B
- Defects in vitamin B12 metabolism

Secondary HUS

- Antiphospholipid syndrome
- Systemic lupus.
- Drugs (Cyclosporin ,chemotherapy)
- Bone marrow transplantation

Pathogenesis

Toxins (bacterial & others) → ++ Leucocytes → ↑ tumor necrosis factor & interleukin 2



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Clinical picture

- Common age: most common in preschool and school-aged children
- Acute diarrhea (often bloody) or respiratory infection is followed few days later by :
 - Acute hemolysis → Acute pallor, jaundice and purpura
 - Acute renal failure → Oliguria, edema, hypertension, acidotic breathing.
 - Hematuria and may be hemoglobinuria
- Genetic forms
 - Onset is insidious
 - Triggered by a variety of illnesses, including mild, nonspecific gastroenteritis or respiratory tract infections
- Complications:
 - Acute renal failure
 - Acute heart failure (hypervolemia, hypertension, anemia)
 - Acute neurologic dysfunction ; encephalopathy in $\leq 20\%$)

Workup**For diagnosis**

For ARF	<ul style="list-style-type: none"> - High creatinine and blood urea nitrogen - High potassium - Metabolic acidosis (\downarrow pH, \downarrow PaCO₂, \downarrow HCO₃)
For MAHA	<ul style="list-style-type: none"> - Anemia - Reticulocytosis - Negative Coombs test (except pneumococci-induced HUS) - Blood Film: fragmented RBCs (Helmet's cells, shistocytes)
For bleeding	<ul style="list-style-type: none"> - Thrombocytopenia counts usually 20,000-100,000/mm³. - Coagulation profile → Normal (unlike DIC)
Urinalysis	<ul style="list-style-type: none"> - Hematuria and may be hemoglobinuria

For etiology

- History of diarrheal prodrome or pneumococcal infection
- If history is negative, consider evaluation for genetic causes
- Stool culture is often negative in diarrhea-associated HUS (even, risk of developing HUS with intestinal E.Coli 0157:H7 is only 10%)

Differential diagnosis**1. From other causes of intrinsic renal failure****2. From other causes of microangiopathic hemolytic anemia: e.g.**

- Bilateral renal vein thrombosis (Marked renal enlargement , Doppler)
- DIC

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Treatment

i. Prevention

- Adequate cooking of meat (especially Hamburger)
- Isolation of cases to avoid cross infection with E.coli

ii. Curative

- Rules of management
 - Early recognition of the disease
 - Monitoring for potential complications
 - Meticulous supportive care
- **ARF**
 - Meticulous fluid and electrolyte management
 - Early dialysis or hemofiltration is usually indicated
 - Treatment as for intrinsic acute renal failure
- **Packed RBCs**
 - May be repeated in active phase as hemolysis take up to 2 weeks
 - For hemoglobin < 6 gram/dl
 - In pneumococci-associated HUS use washed red cells (remove residual plasma containing IgM directed against T antigen)
- **Platelets**
 - Should generally not be administered (consumed by the active coagulation and can theoretically worsen the clinical course)
 - Considered only if elective surgery is indicated or with ICH
- **Others**
 - Antibiotics can result in increased toxin release, potentially exacerbating the disease. It is not recommended except for any underlying pneumococcal infection
 - Plasma infusion or plasmapheresis is considered for serious CNS involvement and in atypical HUS
 - **Eculizumab**; Mono clonal antibody against C5 is promising in atypical (genetic) HUS, even in patients resistant to plasma therapy.

Prognosis

- ✓ Course is unpredictable
- ✓ HUS can be relatively mild or can progress to a severe, and even fatal, multisystem disease
- ✓ More than 50% require dialysis ; 5% remain dependent on dialysis, and up to 20-30% are left with some level of chronic renal insufficiency.
- ✓ Patients who have recovered completely, with no residual urinary abnormalities after a year, are unlikely to manifest long-term sequelae

Alport Syndrome

Definition

- Multisystem disorder : Hereditary nephritis, sensineural deafness and often eye abnormalities
- Classical Alport syndrome is due to mutations in α chain of type IV collagen (COL4); a major component of basement membranes.

Genetics

- Mainly X- Linked disease (85%) caused by a mutation in the COL4 α 5 gene; some are associated with diffuse leiomyomatosis.
- Autosomal recessive or autosomal dominant form (less common).

Clinical manifestations

i. Renal manifestations

1. Hematuria

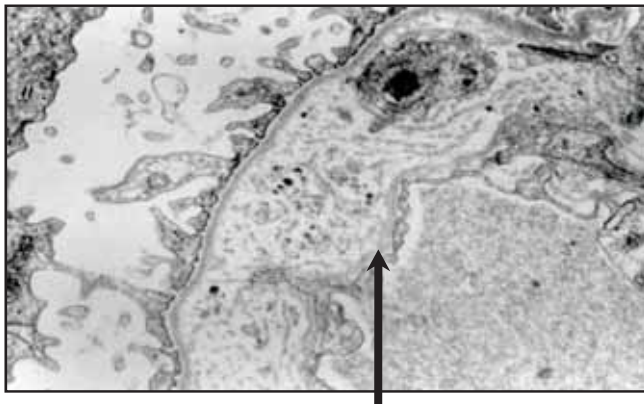
- Affects 100 % of males and 95% carrier females
- Asymptomatic microscopic hematuria, which may be intermittent
- Recurrent gross hematuria*

2. Proteinuria

- Common in males; may be absent, mild, or intermittent in females.
- Progressive by the second decade of life

Renal pathology

- Light : non specific
- Electron microscopy



Reveals:

- Diffuse thickening, thinning, splitting of the basement membranes of the glomeruli & tubules
- Lamellation of the basement membrane (basket wave pattern)

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Prognosis

- ESRD occurs before age 30 years in approximately 75% of hemizygotes with X-linked AS.
- Risk factors for progression
 - Gross hematuria during childhood.
 - Nephrotic syndrome.

ii. Extra Renal manifestations**Hearing deficits**

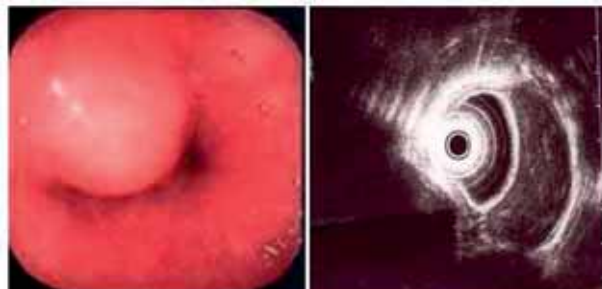
- Affects 90% of males with X-linked AS, less common in cases with autosomal recessive AS, and only 10% of heterozygous females with X-linked AS.
 - Bilateral sensorineural hearing loss (Never congenital in onset)
 - Starts for the high-frequency range but progresses to involve conversational speech
 - Hearing aids are eventual.

**Ocular abnormalities**

- Mainly affects patients with X-linked
 - Anterior *lenticonus* (extrusion of the central portion of the lens into the anterior chamber) is pathognomonic
 - Corneal erosions.
 - Macular flecks.

**Rarely**

- Leiomyomatosis of the esophagus, tracheobronchial tree and female genitalia
- Platelet abnormalities



Endoscopic image of esophageal submucosal leiomyoma and endoscopic US

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Diagnosis

Requirements

- Family history
- Screening urinalysis of first-degree relatives
- Audiogram
- Ophthalmology exam

Diagnostic

- Hematuria *with* anterior lenticonus is pathognomonic
- Hematuria with at least **two** of the following characteristics:
 - Sensorineural deafness
 - GBM thickening and thinning (by EM)
 - Macular flecks
 - Recurrent corneal erosions
- Basement membrane collagen studies.

Note

- Mutation screening or linkage analysis is not clinical use.
- Prenatal diagnosis is available for familial sex linked disease.

Treatment

- ✓ No specific therapy for Alport syndrome.
- ✓ Angiotensin-converting enzyme inhibitors may slow the rate of renal progression.
- ✓ Supportive treatment for renal failure (conservative, dialysis , kidney transplantation); 5% of renal transplant recipients develop anti-GBM nephritis.

Approach to Hematuria

We should exclude other causes of red urine without RBCs by urine analysis (Dipstick) which includes:-

A. Heme positive

- Hemoglobinuria in case of acute hemolytic anemia.
 - CBC shows fragmented RBCs & reticulocytosis
 - Hemoglobin in urine
- Myoglobinuria in case of rhabdomyolysis (myositis, crush)
 - High serum creatine kinase.

B. Heme negative

- Foods e.g. Beet roots, black berries.
- Drugs e.g. Rifampicin, Desferal, Nitrofurantoin.
- Urate crystals (red diaper).

History

- Glomerulonephritis: sore throat/rashes/body swelling
- UTI: fever/frequency/dysuria.
- Renal stones: colicky abdominal pain/family history.
- Coagulopathy: easy bruising.
- Trauma
- Family history: hematuria, deafness (Alport's), sickle cell disease.

Examination

- Blood Pressure (use age,sex and height appropriate blood pressure centiles)
- Abdomen: palpable masses (polycystic kidneys, tumors, hydronephrosis).
- Skin: rashes.
- Joints: pain/swelling.

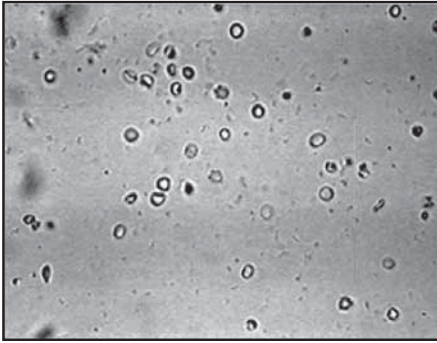
Investigations

- It is important to identify serious, treatable, and progressive conditions.
- During an acute illness, exclude UTI by urine culture.
- Asymptomatic or 'benign haematuria' in children without growth failure, hypertension, oedema, proteinuria, urinary casts, or renal impairment is a frequent finding.

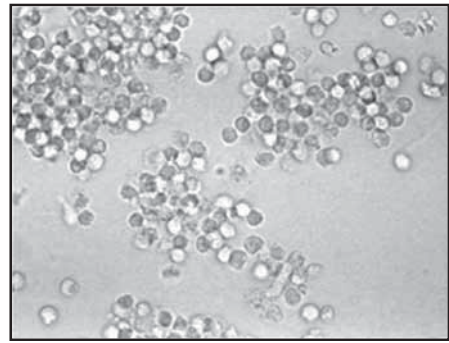
1. Localize hematuria

	Glomerular	Extra glomerular
Acute nephritic syndrome	Present	Absent
Color	Cola or tea colored	Bright red
Clots	Absent	May present
RBCs Shape	Dysmorphic (distorted)	Normal
RBCs casts	Present	Absent
Proteinuria	> 30 mg / dL.	< 30 mg / dL.

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Typical appearance of RBCs in glomerular hematuria: RBCs are small and vary in size, shape, and hemoglobin content



Typical appearance in non-glomerular hematuria: RBCs are uniform in size and shape, along with numerous polymorphs

(Consensus Statement on Evaluation of Hematuria, Indian Pediatrics 2006)

2. For Glomerular hematuria:

▪ Hematology

- CBC with differential

▪ Chemistry

- Electrolytes, Ca
- BUN/ Creatinine /Creatinine clearance
- Serum protein/Albumin /Cholesterol
- Urine protein

▪ Immunology

- C3/C4
- ASO/Anti-DNase B
- ANA
- Antineutrophil antibody

Reduced C ₃ in	<ul style="list-style-type: none"> - Post infectious glomerulonephritis - Systemic lupus nephritis (and low C₄) - Nephritis with chronic infection - Membrano proliferative glomerulonephritis
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3. Renal Biopsy

- Unexplained persistent or recurrent gross hematuria
- Lupus nephritis
- Glomerulonephritis with:
 - nephritic nephrosis
 - Absent low C₃
- Unexplained acute renal

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4. For extra glomerular hematuria**Step 1**

- Urine culture

Step 2

- Urine calcium/creatinine ratio
- Sickle prep (African American)
- Renal/bladder ultrasound

Step 3

- Urinalysis: siblings, parents
- Serum electrolytes, Cr, Ca
- If crystalluria, urolithiasis, or nephrocalcinosis: 24-hour urine for Ca, creatinine, uric acid, oxalate
- If hydronephrosis/pyelocaliectasis: Cystogram, renal scan

(Nelson textbook of pediatrics)

Treatment

- If obvious cause (e.g. UTI), treat.
- If complex diagnosis (impaired renal function, proteinuria, or family history) refer to paediatric nephrology unit.
- If no cause found and normal renal function, BP, and no proteinuria, monitor until resolves.
- If no resolution after 6mths or change in any of above parameters refer to paediatric nephrology unit.

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Proteinuria

Normal values

- Most of the proteins filtered by the *glomeruli* are reabsorbed by the *proximal convoluted tubules*.
- The normal daily urinary protein loss is $< 4 \text{ mg/m}^2/\text{hr}$ or $< 150 \text{ mg/24hr}$.

Detection

1. Urine dipstick analysis (Albustix)

- Less sensitive; affected by urine specific gravity and pH.
- Primarily detects albuminuria ; less sensitive for other forms of proteinuria
- Reported as:
 - Negative
 - Trace (10-20mg/dl)
 - 1+ (30 mg/dl)
 - 2+ (100mg/dl)
 - 3+ (300 mg/dl)
 - 4+ (1000–2000mg/dl)



2. Timed (24-hr) urine collections

- Quantitative for proteinuria (not practical)
- Normal value $< 4 \text{ mg/m}^2/\text{hr}$.
- Abnormal $4 - 40 \text{ mg/m}^2/\text{hr}$.
- Nephrotic range $> 40 \text{ mg/m}^2/\text{hr}$ or $> 50 \text{ mg/kg}$

3. Spot urine protein: creatinine ratio (UPr: UCr)

- Quantitative for proteinuria and more practical timed urine collections
- Use early morning urine sample
- Normal value < 0.5 (< 0.2 in children $\geq 2 \text{ yr}$)
- Nephrotic-range proteinuria > 2

Causes of proteinuria

i. Transient proteinuria (Never exceed 2+):

- Postural or orthostatic : Proteinuria in upright posture only.
- Non postural: - Fever, vigorous exercise, seizures

ii. Persistent proteinuria

	Tubular	Glomerular
Due to	Decreased reabsorption of filtered proteins.	Increased glomerular basement membrane (GBM) permeability.
Level	Usually $< 1 \text{ gm/24 hours}$	Can exceed 1 gm/24 hours
Type	Low molecular weight proteins	Low and high molecular weight proteins
Albuminuria	Absent.	Present.
Associations	Other proximal tubular defects e.g glucosuria, phosphaturia	Edema. May be hypertension, hematuria.
Causes	Fanconi syndromes (Cystinosis, Lignac,.....)	- Damage to GMB, e.g. GN - Dysfunction of GBM e.g.: Minimal change nephrotic syn.

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Nephrotic Syndrome

Definition: Clinico-laboratory condition characterized by:-

- Nephrotic range proteinuria defined as urinary proteins $> 40 \text{ mg/m}^2/\text{hr}$ or a first morning protein : creatinine ratio of $> 2-3 : 1$
- Hypoalbuminemia
- Generalized edema

Hyperlipidemia

Incidence: 15 times commoner in children than adults

Causes of Nephrotic Syndrome

1. Idiopathic (? Lymphocyte dysfunction → altered GBM permeability)

- 90% of cases
- Histologic types
 - Minimal change disease (85%)
 - Focal segmental glomerulosclerosis
 - Membranous nephropathy

2. Genetic nephrotic syndrome

- Finnish-type congenital nephrotic syndrome (absence of nephrin)
- Focal segmental glomerulosclerosis (podocin, actinin mutations)
- Diffuse mesangial sclerosis (laminin mutations)
- Denys-Drash syndrome (mutations in WT1 transcription factor)

3. Secondary nephrotic syndrome

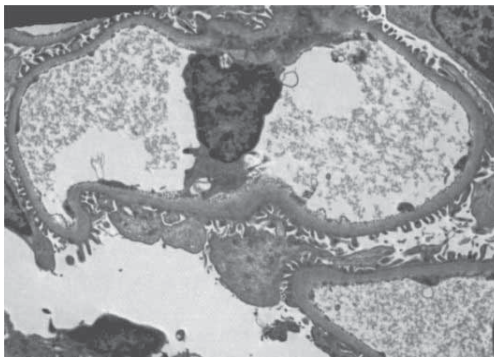
Due to	Examples
Glomerulonephritis with heavy proteinuria	<ul style="list-style-type: none"> - Systemic lupus nephritis - Henoch Schonlein purpura
Infection	<ul style="list-style-type: none"> - Hepatitis B, C - HIV-1 - Malaria - Syphilis - Toxoplasmosis
Allergy	<ul style="list-style-type: none"> - Serum sickness - Bee sting
Drugs	<ul style="list-style-type: none"> - Penicillamine - Gold salts - Interferon - Nonsteroidal anti-inflammatory drugs
Diseases	<ul style="list-style-type: none"> - Sickle cell disease - Amyloidosis - Thrombosis of renal veins
Tumors	<ul style="list-style-type: none"> - Hodgkin lymphoma /Leukemia

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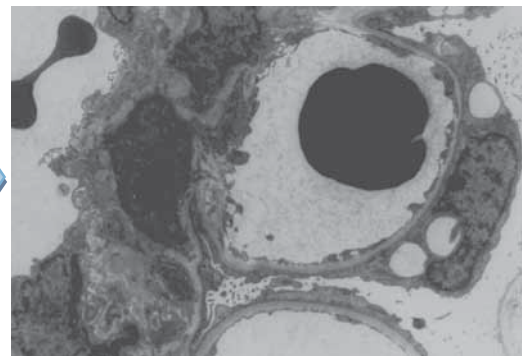
Histological classification

1. Minimal change nephrotic syndrome (MCNS)

- Light microscopy and immunofluorescence → normal.
- Electron microscopy → loss of podocytes foot processes.
- Proteinuria is selective
- Steroid responsive in > 95%.
- In prolonged cases as in relapses or resistance to treatment → more notable changes are seen as focal glomerulosclerosis



Electron microscopy photo of a normal glomerulus with epithelial cells with normal loose foot processes



Electron microscopy photo of a glomerulus in MCNS showing diffuse effacement of epithelial foot processes

2. Focal segmental glomerulosclerosis (FSGS):

- Light and electron microscopy → Segmental sclerosis
→ Focal sclerosis
- Steroid responsive in < 20%.

3. Mesangial proliferative glomerulonephritis

- Light and electron microscopy → increase mesangial cells & matrix.
- Steroid responsive in < 50%.

4. Membranous

- Light & electron microscopy:
 - Uniform thickening of glomerular basement membrane
 - Focal sclerosis as the disease progress

Idiopathic Nephrotic Syndrome

Pathogenesis

1. Proteinuria

* Due to increased glomerular basement membrane (GBM) permeability
(Due to defect in size or altered negative charges of GBM barriers)



Proteinuria is either

- Selective = escape of low molecular weight proteins **as** albumin.

- Non selective = escape of both low & high molecular weight proteins



2. Hypoproteinemia

Decreased total serum proteins → basically hypoalbuminemia

3. Hyperlipidemia



Mainly hypercholesterolemia.

Due to

Hypoproteinaemia

↓ lipoprotein
Lipase

↓ Lipid
catabolism

↓
Stimulate
the liver

↓
↑ Protein synthesis
including lipoproteins

4. Generalized oedema



Due to ↓ plasma osmotic pressure
(↓ proteins & albumin)



fluid shift to interstitial tissue
(mainly in lax & gravity dependent)



↓ intra vascular volume



↑ ADH

↓ Renal blood flow

↓
++ JGA

↓
↑ Aldosterone

↓
Salt and water retention

↓
Water retention

More oedema.

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Clinical picture

- ✓ Peak age in MCNS =2-7 years/ Boys: Girls 2:1
- ✓ The initial episode and relapses may follow viral upper respiratory tract infection.

1. Generalized edema

- Start as morning periorbital puffiness then progress to involve lower limbs, genitalia and abdominal wall with stretched skin and skin breaks
- Oedema is very soft, pitting,
- Ascites and pleural effusion are very common → may be respiratory distress.
- With developing edema and increasing weight → urine volume is declining



2. Gastro intestinal mucosal oedema → anorexia, abdominal pain & diarrhea
3. Hypertension may occur in only 5-10%.

Complications**1. Hypovolemia**

- **Precipitated by**

- Sepsis
- Diarrhea
- Use of diuretics



- **Presentation**

- Abdominal pain
- Hypotension
- Poor perfusion
- Hemoconcentration

2. Acute renal failure (Nephrotic crisis)

- **Precipitated by**

- Severe hypovolemia → ↓↓ renal blood flow (pre renal failure).
- Renal vein thrombosis.
- Sepsis

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3. Intra vascular thrombosis

▪ **Precipitated by**

- Hypovolemia → hemoconcentration → sluggish circulation
- Increased platelet adhesiveness and certain coagulation factors.
- Decreased natural anti-coagulants e.g. Anti thrombin III and protein C.

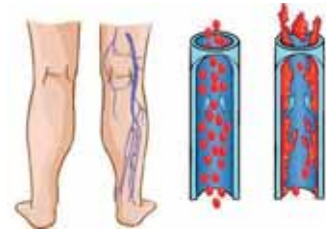
▪ **Common sites**



Cerebral cortical veins



Renal veins



Deep venous thrombosis

4. Infections

▪ **Precipitated by**

- Loss of immunoglobulins and complement factor B
- Edema or ascites acting as a potential culture medium
- Immuno suppressive therapies

▪ **Common infections:** basically by capsulated bacteria and viruses

- Spontaneous bacterial peritonitis (*Strept. pneumoniae*, *E.Coli*)
 - ✓ Child looks ill, feverish with persistent abdominal pain
 - ✓ Prompt evaluation (including cultures of blood and peritoneal fluid), and early initiation of antibiotic therapy are critical.
- Others: urinary tract infections (*E.coli*), pneumonia (*H. influenza*), cellulitis (*Staph aureus*), and sepsis

5. Relapse

- Recurrence of significant proteinuria ;urine Albustix ++ or more for 3 consecutive days
- Frequent Relapsing Nephrotic Syndrome (FRNS): Relapses 4 or more within 12 months period.
- Steroid Dependent Nephrotic Syndrome (SDNS): nephrotic syndrome that relapses during steroid tapering or immediate after steroid withdrawal.

6. Complications in Resistant and FRNS

- Protein depletion: muscle wasting, osteoporosis, short stature
- Chronic renal failure → in non- MCNS
- Drugs complications: *See later*

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Investigations

1. For diagnosis

A. Urine analysis

- Heavy Proteinuria:
First morning protein: creatinine ratio of >2-3: 1 (Timed urine protein > 40 mg/m²/hr)
- Color: Yellowish, frothy
- Specific gravity: High
- Waxy (lipoid) & hyaline casts.
- Microscopic hematuria in about 10% of MCNS.

B. Biochemical

- Low serum albumin < **2.5** gm/dl (normal: 3.5 - 4.5 gm/dl),
Low total proteins < **4.5** gm/dl. (normal :6.5 - 8 gm/dl)
- Increased serum cholesterol > **220** mg/dl
- Complement C3 and C4 levels (Normal in MCNS)

2. Workup before starting therapy

- CBC.
- Urine microscopy and culture as there is an increased rate of UTI.
- Infectious disease workup including
 - PPD (Mantoux) skin test and chest X-ray in TB endemic areas.
 - Varicella zoster serology to determine immune status.
 - Hepatitis B and C serology.
- Lupus antibody serology (ANA, extractable nuclear antibodies (ENA), and ds-DNA) in older children, and those with atypical presenting features

3. Renal biopsy

- Not indicated if MCNS is suggested.
- Indications.

<u>Before treatment</u>	<u>After treatment</u>
<ul style="list-style-type: none"> - Age < 1 or >12 years. - Gross hematuria. - Renal failure - Low C3 	<ul style="list-style-type: none"> - Steroid resistance. - Frequent relapsing



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Differential Diagnosis

1. Form other causes of generalized edema (See Clinical)

2. From causes of secondary nephrotic syndrome:

A diagnosis other than MCNS should be considered in

- Children <1 yr of age
- A positive family history of nephrotic syndrome
- Presence of :
 - Extrarenal findings (e.g., arthritis, rash, anemia)
 - Hypertension or pulmonary edema
 - Acute or chronic renal insufficiency
 - Gross hematuria

Treatment of Nephrotic Syndrome

Supportive care

1. Fluid balance, hypovolemia, and blood pressure

- Mild peripheral edema:
 - Do not require fluid restriction
- Significant edema
 - Mild fluid restriction (70 % of maintenance requirements)
 - A low salt diet control thirst and minimizes edema
- Regular assessment of temperature, weight, BP, hydration state

2. Avoid infections

- Avoid contact with infectious patients
- Broad spectrum Antibiotics for any current infections pending bacterial cultures
- Nonimmune child, if exposed to Varicella, should receive varicella-zoster immunoglobulin dose within 4days after significant exposure.
- Edematous child should receive prophylactic penicillin V 12.5mg/kg bd
- Vaccines :
 - ✓ Routine vaccines should be given during remission
 - ✓ Live vaccines should only be administered when the child is off all immunosuppressive therapy (*1 month following discontinuation of steroids and 3-6 months following discontinuation of cyclosporine and cyclophosphamide*).
 - ✓ Other recommended vaccines: Pneumococcal(both types) , H. influenza vaccines and annual influenza/H1N1 vaccine

3. Avoid thrombosis

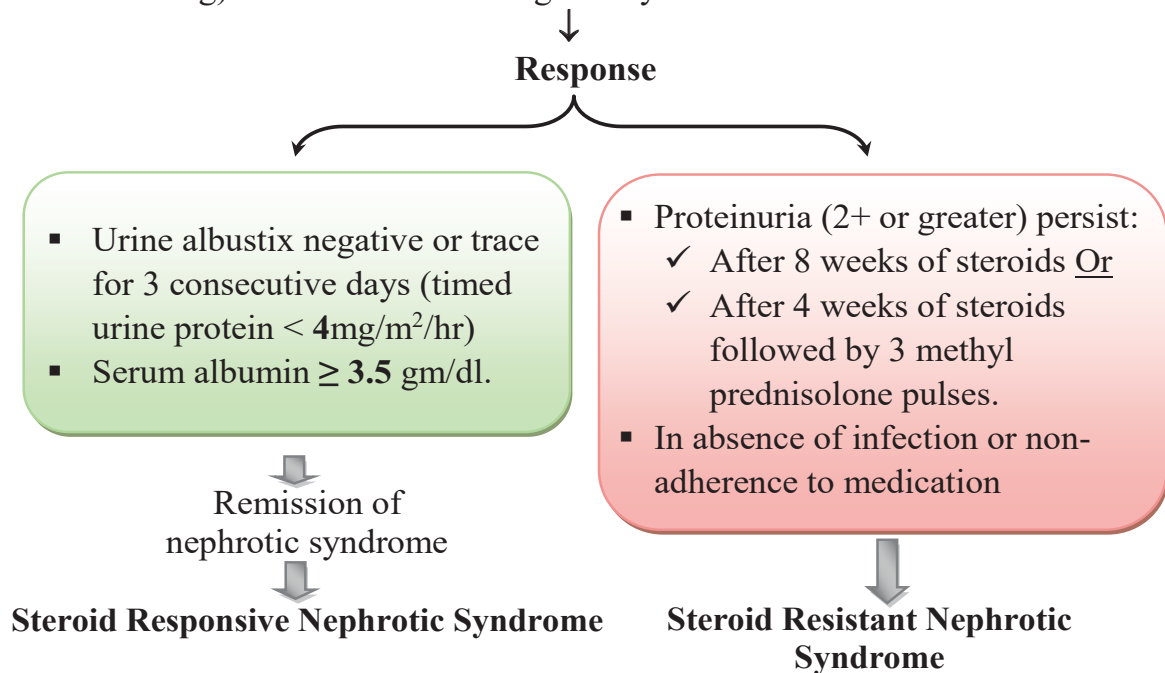
- Low dose aspirin
- Treat hypovolemia either by:
 - Plasma 20 ml /kg or
 - 4.5 % albumin solution 10 – 20ml/kg
 - Diuretics should be stopped or avoided in this setting

4. Salt free albumin

Indications	Massive generalized oedema (anasarca) with respiratory difficulty
Precaution	May cause acute increase of intravascular volume <i>so</i> observe closely for developing hypertension or heart failure
Dosage	<ul style="list-style-type: none"> - Up to 1g/kg (up to 5mL/kg 20 % albumin) - Should be infused slowly over 4h - Furosemide 1–2mg/kg being given IV during the second half of the infusion

Specific therapy

Induction of remission by **Prednisone** 60 mg/m²/d or 2 mg/kg/d (maximum dose 80mg) for 4 weeks in a single daily dose



1. Steroid Responsive Nephrotic Syndrome:

After the initial 4 weeks induction:

- Use alternate day prednisone 40 mg/m² as single morning dose for 4 weeks
- Followed by gradual withdrawal over 4 months with monitoring for proteinuria

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Suggested plan:

- 40 mg/m² (-1.5 mg/kg) Q48 hours for 4 weeks, then
- 20 mg/m² (-0.75 mg/kg) Q48 hours for 4 weeks, then
- 10–15 mg/m² (0.5 mg/kg) Q48 hours for 4 weeks, then
- 5–7.5 mg/m² (0.25 mg/kg) Q48 hours for 2 months

(Manual Of Pediatric Nephrology)

Outcomes

- No relapses (30%) → Observe
- Relapse > 3 months after steroid withdrawal → Re treatment as above
- Relapse while on alternate day steroid therapy or < 28 days after steroid withdrawal are termed steroid dependent nephrotic syndrome ; 60%



* Re induction followed by alternate day steroids

* Then to minimize relapse rate try the following:

- 1- Prolong alternate day steroid therapy for up to 12-18 months
- 2- Steroid sparing therapies:

▪ Levamisole	2.5 mg/kg Every 48H for 12 months
▪ Cyclophosphamide	2 mg/kg/day for 12 week
▪ Cyclosporine (CSA)	5–7 mg/kg/day
▪ Mycophenolate Mofetil (MMF)	600–1200mg/m ² /day 12 months
▪ Tacrolimus(Prograf)	0.1–0.2/kg/day or at least 12 months
▪ Rituximab	Every 4–6 months 375 mg/m ² per infusion

2. Steroid resistant nephrotic syndrome: may benefit from

- Methylprednisolone pulses with cyclophosphamide (Mendoza protocol).
The recent guidelines advise against this protocol for SRNS.
- Steroid pulse therapy :
 - Methylprednisolone 10 mg/kg or 300 mg/m² IV infusion every other day for 3 doses followed by Prednisone 40 mg/m² every other day.
 - Kidney biopsy and genetic testing are essential to avoid excess glucocorticoid toxicity
- Steroid sparing medicines: Cyclosporine , Tacrolimus, MMF
- Anti proteinuric agents: ACE inhibitors and Angiotensin II Blockers (ARBs)
- Supportive therapy
 - Lipid-lowering drugs
 - Thrombosis prophylaxis
 - Vitamin D
- Renal transplantation

(Oxford Pediatric Nephrology)

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N.B Drugs Complications

Steroids

- Cataract
- Ulcers (peptic) → add ranitidine or proton pump inhibitor
- Striae
- Hypertension
- Infections due to immunosuppression
- Necrosis of bone → may require calcium and vit D
- Growth retardation → monitor height Q 3 months
- Osteoporosis
- Intracranial hypertension
- Diabetes Mellitus
- Myopathy (proximal)
- Adipose tissue hypertrophy (moon face, Buffalo hump, trunkal obesity)
- Pancreatitis



Cyclophosphamide

- Alopecia
- Bone marrow suppression
- Hemorrhagic Cystitis (prevented by I.V. Mesna)
- Decreased fertility

Cyclosporin A

- Hypertrichosis
- Hypertension
- Hyperplasia of gums
- Nephrotoxicity

MMF

- Leucopenia /anemia
- GIT ulcerations

Tacrolimus

- Hyperglycemia
- Nephrotoxicity

Rituximab

- Immunosuppression
- Unclear long term safety profile

Causes of death in nephritic syndrome?

1. Renal failure
2. Overwhelming infections
3. Hypovolemic shock

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Congenital and infantile nephrotic syndrome

- Congenital nephrotic syndrome (CNS):
Presentation of nephrotic syndrome during the first **3** months of life (often present before or at birth)
- Infantile nephrotic syndrome :
Presentation of nephrotic syndrome between **3** and **12** months of age

Primary causes

- Finnish-type CNS
- Diffuse mesangial sclerosis
- Focal segmental glomerulosclerosis
- Membranous nephropathy
- Minimal change disease

Secondary causes

- Congenital Infections
- Syndrome-associated:
 - Denys Drash syndrome: Wilm's tumor, genitourinary anomalies , nephrotic syndrome
 - Nail-patella syndrome
 - Lowe's syndrome
 - Frasier syndrome : Male pseudohermaphroditism and proteinuria

Other: e.g.

- HUS
- Nephroblastoma
- Drug reaction

Fennish type congenital nephrotic syndrome

- Autosomal recessive disorder
- Most patients have mutations in the NPHS1 gene which encodes for *Nephrin* protein in the glomerular basement membrane.

Presentation

- Low birth weight
- Large edematous placenta (> 25 % mass of newborn)
- Generalized edema
- Histology: early tubular dilatation (microcytic change), later on glomerular sclerosis and fibrosis ending in end stage renal failure

Treatment

- Bilateral nephrectomies and peritoneal dialysis + Transplantation once the child has reached approximately 9 –10kg
- Alternatively, perform early unilateral nephrectomy plus medical therapy + Second nephrectomy and subsequent transplantation at 3 – 4 years of age

Medical supportive therapy (as before)

- Regular albumin infusions via a central venous catheter until bilateral nephrectomy is performed
- ACEI/ARBs.
- NSAID e.g. Indomethacin up to 4mg/kg divided into three doses.
- Thyroxine is necessary from birth.
- Childhood vaccines should be completed after nephrectomy prior to transplantation
- Close attention to nutrition and growth — high calorie and high protein diet (4mg/kg/day).
- Anticoagulation with warfarin/aspirin may have a role.

(Oxford pediatric nephrology handbook)

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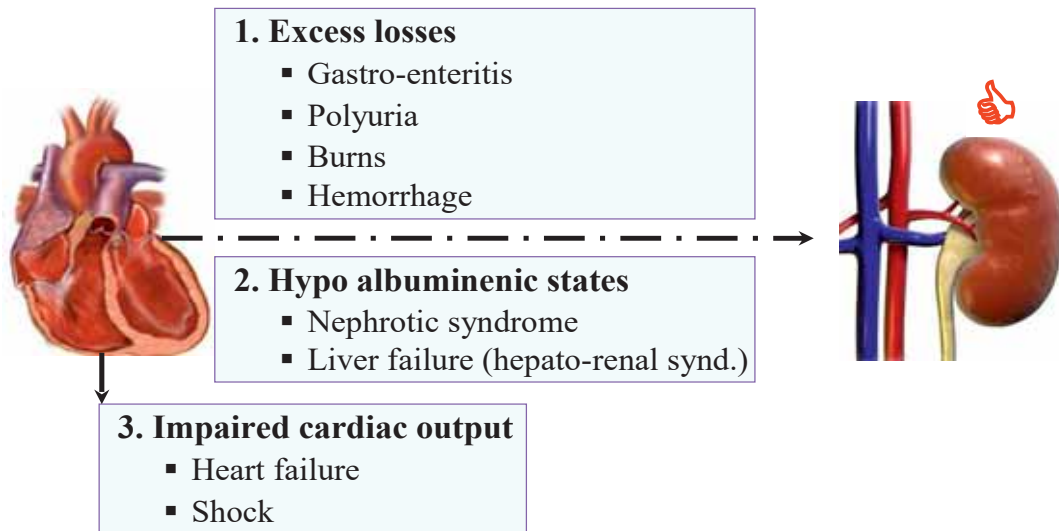
Acute Renal Failure (ARF)

Definition: A sudden, potentially reversible inability of the kidney to maintain normal body chemistry and fluid balance. The term ARF has been replaced by the term Acute Kidney Injury (AKI).

Etiology

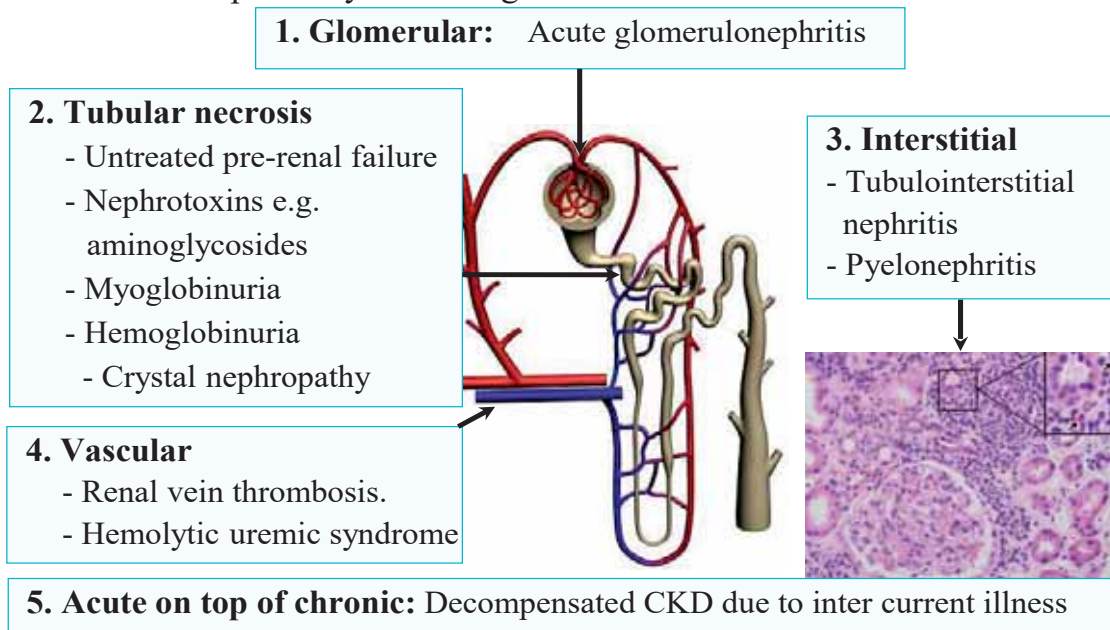
A. Pre renal (60%)

Due to: Marked reduction of renal blood flow



B. Intrinsic renal (30%)

Due to: Renal parenchymal damage



C. Post renal (10%): Due to: urine outflow obstruction (Obstructive uropathy)
By stones, tumors, trauma

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Clinical picture

1. Manifestations of the cause; basically in pre renal failure

2. **Oliguric phase:**

Mechanism	Clinical sign
Water retention	<ul style="list-style-type: none"> – Oliguria or anuria – Edema – Hypertension
Waste retention	<ul style="list-style-type: none"> – Acidotic breathing (rapid & deep) – Hyperkalemia → dysrhythmias – Urea → uremic encephalopathy (confusion → convulsions → coma)
Systemic upset	<ul style="list-style-type: none"> – Heart failure up to acute pulmonary edema may occur due to hypervolemia – GIT bleeding may occur due to gastric stress ulcers and thrombocytopenia – Convulsions may occur due to excessive salt loss(hyponatremia) or uremic encephalopathy

3. **Polyuric phase:**

It may occur indicating early recovery → new tubular cells can't retain fluid & electrolytes → polyuria & electrolyte loss.

Diagnosis**1. Is there an Acute Kidney Injury**

<ul style="list-style-type: none"> ▪ Urine volume 	<ul style="list-style-type: none"> – Oliguria: <ul style="list-style-type: none"> ▪ Urine output < 0.5mL/kg/h (< 300 ml/m²/day) or ▪ < 1mL/kg/h in an infant – Anuria : urine output < 30 ml/m²/day
<ul style="list-style-type: none"> ▪ Renal function tests 	<ul style="list-style-type: none"> – Elevated serum creatinine – Elevated urea & blood urea nitrogen(BUN)
<ul style="list-style-type: none"> ▪ Acid / base disturbance 	<ul style="list-style-type: none"> – Metabolic acidosis (↓pH, ↓PaCO₂, ↓HCO₃).
<ul style="list-style-type: none"> ▪ Electrolytes 	<ul style="list-style-type: none"> – Hyperkalemia. – Hyponatremia. – Hypocalcemia, hyperphosphatemia

Creatinine is an insensitive and delayed measure of decreased kidney function. Other biomarkers under investigation include changes in plasma neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C levels and urinary changes in NGAL

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2. For effect/cause

- a) ECG: for evidence of hyperkalemia
 - Tall peaked T wave; the earliest ECG sign of hyperkalemia
 - Widening of QRS complex
 - Arrhythmias
- b) Ultrasonography
 - Exclude obstructive uropathy
 - Differentiate between acute (enlarged and echobright kidneys) and acute on top of chronic failure (shrunken kidneys)
- c) Radiologic studies:for
 - Heart failure: cardiomegaly with prominent pulmonary markings
 - Renal stones

3. Diagnosis of the type

i. Post renal

- 1- Palpable bladder & kidneys.
- 2- Bladder catheterization
- 3- Abdominal ultrasound to exclude obstructive uropathy.

	ii. Pre renal	iii. Intrinsic renal
Clinical	Hypovolemia : <ul style="list-style-type: none"> – Tachycardia – Core-peripheral temperature gap > 2 °C – Prolonged capillary refill time – Dehydration – Hypotension 	Euolemia <u>or</u> Hypervolemia : <ul style="list-style-type: none"> – Hypertension – Raised jugular venous pressure – Tachycardia, gallop rhythm – Palpable liver
Laboratory <ul style="list-style-type: none"> ▪ Urine osmolality ▪ Urine specific gravity ▪ Urine sodium ▪ Fractional excretion of Na(FNa) ▪ BUN / creatinine ratio(mg/dl) 	High <ul style="list-style-type: none"> > 1020 < 20 meq/L < 1 > 20:1 	Low <ul style="list-style-type: none"> < 1010 > 30 meq/L > 1 10-20:1 (+ oliguria)
US	Normal	Kidneys are enlarged and echobright

Pediatric RIFLE (pRIFLE) criteria

Used for the detection and classification of AKI and for correlation with clinical outcomes

	Serum creatinine rise	GFR decline	Urine out put
Risk	1.5-fold	25 %	<0.5 ml/kg/h × 8 h
Injury	2-fold	50 %	<0.5 ml/kg/h × 16 h
Failure	3-fold	75% or < 35 ml/min/1.73 m ²	<0.3 ml/kg/h × 24 h or anuric for 12 h
Loss	Persistent failure > 4 weeks		
End stage	ESRD (persistent failure >3 months)		

Treatment of ARF**I. Hospitalization and Monitoring**

- Weight → Twice daily
- Fluid input-output recording → Hourly
- Vitals; including BP → Hourly
- Blood sugar → 6-hourly
- Neurological observations → Hourly
- Renal parameters (BUN/Creatinine) → May be appropriate to perform up to every 6hours
- Blood gases, Electrolytes

II. Correct Post-renal causes

→ Remove obstruction (by catheterization ± surgical)

III. Correct pre-renal causes

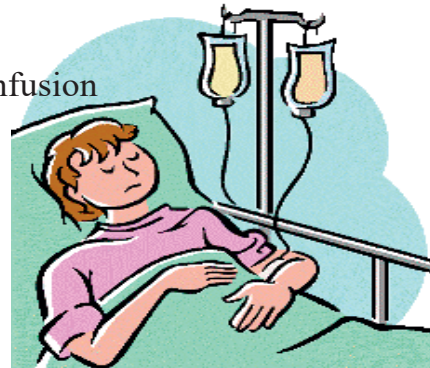
- Fluid resuscitation → Restores renal blood flow



- Fluid loss → saline infusion 10 ml/kg over 30 minutes
- Blood loss → fresh blood transfusion
- Plasma loss → plasma transfusion
- Protein loss (Nephrotic) → albumin infusion



- Repeat if necessary
- With good correction → the patient should void within 1-2 hours



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IV. Treatment of intrinsic renal failure

1. Monitoring

2. Maintain fluid balance:

Euvolemic	<ul style="list-style-type: none"> – Fluid challenge 10–20mL/kg normal saline over 1h <u>with</u> – Furosemide 2–4mg/kg IV
Hypervolemic	<ul style="list-style-type: none"> – Furosemide 2–4mg/kg IV

- Maximum dose of diuretic = 12mg/kg/day
- Value : Reduce volume overload & enhance potassium excretion
- If there is no response to a diuretic challenge, diuretics should be discontinued and start fluid restriction / Dialysis

Fluids intake

- Daily intake = insensible loss (400 ml/m² or 30mL/kg/day) + plus urine output and other ongoing losses
- Type: feeds if tolerated or IV D5 / Half normal saline
- Replace 100 % of urine output if euvolemic.
- Restrict to 50–75 % of urine output if overloaded

Nutrition

- Consult renal dietician
- Maximize caloric intake
- Restrict sodium, potassium and phosphorus and proteins

3. Management of electrolyte and acid base abnormalities

a. Hyperkalemia (potassium level ≥ 6 meq/L):

- Restrict potassium intake
- Enhance GIT excretion by kayexalate (polystyrene resin) oral or enema.
- With potassium levels above 7 meq/l or ECG changes appear
 - Stabilize cardiac membrane by 1 ml/kg calcium gluconate 10% slow I.V
 - Shift potassium intracellular by:
 - Salbutamol nebulizer
 - Sodium bicarbonate 1-2 mEq/kg over 10 minutes i.v
 - Regular insulin(0.1 u/kg) + glucose 50% solution(1 ml /kg) over 1 hour
- Persistent hyperkalemia should be managed by dialysis

b. Hyponatremia (sodium level < 130 meq/L):

- Dilutional hyponatremia usually respond to fluid restriction
- Hyponatremia < 120 meq/l with seizures is treated with Na CL 3% (Target serum sodium 125 mEq/l)

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c. Hypocalcemia and hyperphosphatemia

- Tetany is rare as acidosis increases ionized calcium.
- Restrict phosphate intake & give phosphate binders e.g. sevelamer (Renagel), calcium carbonate or calcium acetate (PhosLo).
- Calcium gluconate 10 % slow iv only for cases with tetany

d. Metabolic acidosis

- Slow partial correction with IV bicarbonate 1–2mmol/kg
- Monitor serum calcium

4. Treatment of complications

- Anemia → Fresh packed RBCs transfusion over 4 - 6 hours
- Hypertension → Diuretics, Isradipine , amelodipine etc

5. Dialysis

Indications

Clinical

1. Volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy
2. Neurologic symptoms (altered mental status, seizures)
3. Inability to provide adequate nutritional intake because of the need for severe fluid restriction(dialysis provides a space for nutrition)

Laboratory

1. Persistent hyperkalemia
2. Severe metabolic acidosis unresponsive to medical management
3. Blood urea nitrogen >100-150 mg/dL (or lower if rapidly rising)
4. Calcium: phosphorus imbalance, with hypocalcemic tetany

Modes of dialysis

- 1) Peritoneal dialysis : most commonly employed in neonates and infants with ARF
- 2) Continual Renal Replacement Therapy (CRRT): useful in patients with unstable hemodynamic status, concomitant sepsis, or multiorgan failure in the intensive care setting
- 3) Intermittent hemodialysis: useful in patients with relatively stable hemodynamic status

Prognosis

- ❖ The mortality rate depends entirely on the nature of the underlying disease
- ❖ Recovery of renal function is likely after ARF resulting from prerenal causes, HUS, Acute tubular necrosis, or acute interstitial nephritis.
- ❖ Poor outcome with AKI following rapidly progressive glomerulonephritis, bilateral renal vein thrombosis, or bilateral cortical necrosis

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Chronic kidney disease (CKD)

Chronic Renal Failure (CRF)

Definition

- Irrecoverable, bilateral abnormalities of the renal parenchyma → permanent reduction of glomerular filtration rate (GFR)
- CKD has replaced “chronic renal failure” and “chronic renal insufficiency” as the globally accepted terminology for persistent renal dysfunction

Stages of CKD

CKD stage	Description	GFR (ml/min/1.73 m ²)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	<15 (or dialysis)

(Manual of pediatric nephrology)

Causes

In < 5 years of age

- Congenital malformations:
 - Hypoplastic/dysplastic kidneys
 - Reflux nephropathy(VUR+UTI)
 - Obstructive uropathy
- Metabolic/genetic disorders:
 - Oxalosis
 - Polycystic kidney disease
 - Congenital nephrotic syndrome
 - Wilms' tumor

In > 5 years of age

- Glomerular disease:
 - Focal segmental glomerulosclerosis
 - Hemolytic uremic syndrome
 - Chronic glomerulonephritis
 - Alport's syndrome
- Tubulointerstitial disease:
 - Chronic tubulointerstitial nephritis
 - Cystinosis
 - Nephrotoxic drugs

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Clinical picture

Non specific so, need high index of suspicion

Clinical feature	Mechanism
○ Growth retardation (Short stature)	- Resistance to growth hormone - Anemia - Anorexia (metabolic acidosis) - Renal osteodystrophy
○ Unexplained anemia	- ↓ Erythropoietin - ↓ intake of iron, B12, folic acid. - Bone marrow depression by uremic toxins - Defective iron utilization.
○ Polyuria / Polydipsia/ Nocturia	- Renal tubular concentration defect
○ Hypertension	- Increased renin & fluid retention
○ Renal osteodystrophy (ROD)	- Hyperphosphatemia - Decreased 1,25 (OH) ₂ D ₃ - Secondary hyperparathyroidism
○ Bleeding tendency	- Platelet dysfunction
○ Infection	- Defective granulocyte function
○ Neurologic (fatigue , drowsiness, polyneuropathy)	- Uremic toxins
○ Pericarditis, cardiomyopathy	- Uremic toxins - Hypertension
○ Hyperlipidemia	- ↓ lipoprotein lipase activity
○ Hyperkalemia and hyponatremia	

Diagnosis

1. Assessment of renal function:

- Serial measurements of creatinine: An abnormal serum creatinine value persisting for more than 3 months confirms CKD.
- Estimated GFR by Schwartz's equation & DTPA scan
- Proteinuria: Persistent proteinuria is a marker of ongoing renal disease.

2. Renal ultrasound & DMSA scan show shrunken kidneys (Kidneys may appear large e.g. Polycystic kidney disease , Obstructive uropathy)

3. For complications:

- CBC for anemia
- Lipid profile
- Echocardiography for pericardial effusion & cardiomyopathy.
- In ROD → High phosphate - low calcium - high intact PTH
→ Bone X-ray → subperiosteal erosions ± bone cysts.

4. For the cause

5. Follow up investigations (see later)

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Treatment

Stages of treatment:

- Stage 1: diagnosis and treatment of primary disease
- Stage 2- 3: retard progression, treat complications/comorbidities
- Stage 4: prepare for renal replacement therapy
- Stage 5: renal replacement

Outpatient checks in the child with CKD

- Height, weight and head circumference
- Pubertal stage
- BP

Investigations at each clinic visit

1. Full blood count (FBC; and ferritin if needing an erythropoiesis stimulating agent).
2. Urea & electrolytes (U&Es), bicarbonate, and creatinine
3. Calcium, phosphate, albumin, alkaline phosphatase, intact PTH
4. Urine protein or albumin to creatinine ratio
5. Fasting HDL and LDL, total cholesterol and triglycerides 6 monthly.

Management

A. Slowing the progression of chronic kidney disease

1. Control proteinuria
 - Rate of decline of kidney function is closely related to the quantity of proteinuria
 - Use:
 - ✓ Angiotensin Converting Enzyme Inhibitors; enalapril or captopril and/or
 - ✓ Angiotensin Receptor Blockers(Irbesartan)
2. Control hypertension
 - BP should be maintained within the normal range for age and height
 - There is some evidence that BP <50th centile may be beneficial
3. Control Dyslipidaemia by
 - Dietary intervention
 - Statins
4. Treatment of anemia

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B. Conservative treatment

Nutrition

- Consult expert dietician
- Treat vomiting (ranitidine)
- High caloric diet
- Dietary supplements, either orally or enterally, via nasogastric tube or gastrostomy, if anorexic
- Protein and potassium restriction may be needed in stage 4-5 CKD!
- Feeding infants with CKD:
 - Breast milk
 - Special formula e.g. Low salt formula (*SMA*), high energy formula (*Maxijul*), low potassium , low phosphate formula (*Renastart*),...

Fluid and electrolyte balance

- If polyuria→ free access to water
- If salt and bicarbonate loser→ salt and bicarbonate supplementation

Growth

- Correct acidosis, hyperparathyroidism and anemia
- Optimize nutrition
- Recombinant human growth hormone (rhGH)

Anemia

- Target Hb should be in the range of 11.0–12.0 g/dl
- Iron supplement
- Erythropoietin 50-100 U/kg/week or Darbepoetin α (longer half-life)
- RBCs Transfusion for symptomatic severe anemia

Mineral and bone disorder (ROD)

- **The target range of serum PTH is closely related to stage of CKD**
- Treatment
 1. Control hyperphosphatemia
 - Dietary phosphorus restriction
 - Phosphate binders; administered with meals
 - Calcium based e.g. Calcium carbonate, calcium acetate
 - Non calcium based: Sevelamer (*Renagel*) is now more popular
 2. Maintain serum calcium
 3. Vitamin D therapy: One Alpha = 1 α (OH) D3 and Calcitriol
 4. Ca sensing receptor blockers, *Cinacalcet*, blocks calcium sensing receptors (CaSR) in parathyroids → Reduce PTH.
 5. Partial parathyroidectomy for treatment - resistant tertiary hyperparathyroidism with persistent hypercalcemia

Hypertension (HTN)

- Target blood pressure should be lower than the 90th percentile for normal values adjusted for age, gender, and height
- Maintaining BP below the 50th percentile may be effective in delaying progression of CKD
- Use
 - Diuretics
 - ACEI/ARBs
 - Calcium channel blockers
 - Beta blockers

Immunizations

- All children must complete all routine childhood vaccines.
- BCG, Varicella, pneumococcal polysaccharide (PPV) and hepatitis B vaccines must be added in children approaching RRT
- Annual influenza vaccine
- Transplantation can be delayed till vaccination schedule is completed

C. Renal replacement therapy (RRT)

Dialysis

Indications:

Laboratory criteria:	<ul style="list-style-type: none"> – GFR <15 ml/min/m² – Refractory hyperkalemia, hyperphosphatemia, and metabolic acidosis
Clinical criteria	Children with symptoms of <ul style="list-style-type: none"> – Nausea, vomiting – Malnutrition, growth retardation – Fluid overload, hypertension – Uremia Despite optimal medical management

Types

- Hemodialysis
- Chronic peritoneal dialysis

Renal transplantation

- The renal replacement therapy of choice in children
- Offering a near normal life to a child with end-stage renal disease

Urinary Tract Infections

Urinary tract infections can present as

- Upper urinary tract infections → acute & chronic pyelonephritis
- Lower urinary tract infections → acute & chronic cystitis & urethritis
- Asymptomatic bacteruria
- Septicemia

Causes

Risk factors	Common organisms
<ul style="list-style-type: none"> - Females (short urethra) - Uncircumcised boys - Vesico ureteric reflux(VUR) - Obstructive uropathy - Constipation - Instrumentation 	<ul style="list-style-type: none"> - G -ve → - Escherichia coli (80%) <li style="padding-left: 20px;">- Proteus (more in boys) <li style="padding-left: 20px;">- Pseudomonas - G +ve → staph, strept. fecalis

Causes of recurrent UTI

1. Obstructive uropathy:

- VUR either congenital or secondary to UTI
- Congenital anomalies e.g. phimosis
- Renal calculi
- Neurogenic bladder

2. Catheters or foreign bodies

3. Constipation; elimination disorders

4. Mal treatment or inadequate treatment of an acute attack

Clinical picture: (presentation differs according to age)

Asymptomatic bacteruria: - positive urine culture without manifestations

Newborn	<ul style="list-style-type: none"> - Sepsis (Jaundice, ↓ feeding,
Infant	<ul style="list-style-type: none"> - Fever (UTI is the most common bacterial cause of fever without focus in infants) - Screaming during micturition - Failure to thrive(vomiting→ weight loss)
Child	<ul style="list-style-type: none"> ▪ Lower UTI - Urgency, dysuria, frequency <ul style="list-style-type: none"> - Suprapubic pain - 2^{ry} nocturnal enuresis - May be hematuria ▪ Upper UTI - Acute → Fever, rigors & loin pain <ul style="list-style-type: none"> - Chronic → Prolonged fever <li style="padding-left: 20px;">→ May be hypertension

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Investigations

1. Diagnosis of urinary tract infections: by Urinalysis and culture

Urine sample obtained by:

- *For toilet-trained children*
 - Mid-stream voided urine
 - *For non-toilet-trained children*
 - Clean catch into a waiting sterile pot when the nappy is removed
 - Urine bag (high a rate of contamination → unreliable culture results)
- ↓
- If UTI is suggested; order a urine culture using a sample by either
- ↓
- In and out catheter sample; reliable and more practical than SPA
 - Suprapubic aspiration; SPA (Reserved for sick patients)

Findings

- Pyuria:
 - ≥ 5WBCs/hpf Or ≥ 10 WBCs/ml
 - [Absence of pyuria is rare if UTI is present]
 - Leukocyte esterase and Nitrite tests are usually positive with UTI
 - Gram stained films: For bacteruria
 - *Urine culture*: necessary for confirmation and appropriate therapy
- Minimum colony counts indicative of a urinary tract infection:

Specimen	(CFU/mL)
– Clean catch (midstream)	≥10 ⁵
– Catheter	≥5×10 ⁴
– Suprapubic aspiration	Any growth

2. Indicators of upper UTI (Acute pyelonephritis):

- Leukocytosis, neutrophilia
- Elevated serum erythrocyte sedimentation rate and C-reactive protein
- Blood cultures, particularly in infants and in obstructive uropathy
- DMSA scan

3. Imaging studies:

Imaging tools	Yield
Ultrasound of kidneys and bladder	<ul style="list-style-type: none"> – Assess kidney size , anatomy and position – Evaluate bladder wall thickness and emptying – Detect ureteral dilation – Detect hydronephrosis

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MCUG (Micturating Cyst Urethro Gram)	<ul style="list-style-type: none"> – The gold standard investigation for the diagnosis of urethral abnormalities and VUR – Evaluate bladder anatomy and emptying
Plain abdomen	<ul style="list-style-type: none"> – Fecal masses – Spinal dysraphism
DMSA scan	<ul style="list-style-type: none"> – The gold standard investigation for the diagnosis of renal parenchymal damage <ul style="list-style-type: none"> ▪ Acute : diagnose acute pyelonephritis ▪ Chronic : detect renal scarring

NICE Guideline for imaging in UTI

Ultrasound

- Indicated during the acute infection for:
 - Infants below 6 months
 - Atypical UTI
 - Recurrent UTI

MCUG

- Done at 2-4 weeks post UTI allowing bladder inflammation to resolve
- Indications:
 1. After a second UTI is diagnosed
 2. After a first UTI with:
 - Abnormal ultrasound findings e.g. hydronephrosis, scarring, obstructive uropathy or VUR
 - Poor urine flow
 - Non E.coli UTI
 - Family history of vesico ureteral reflux VUR

DMSA scan

- Done at 4-6 months in order to avoid a false positive result due to renal parenchymal inflammation that may resolve
- Indications:
 - Child > 3 years of age with clinical pyelonephritis
 - Atypical UTI
 - Recurrent UTI

- ✚ In children with infection of the lower urinary tract, imaging is usually unnecessary.
- ✚ Instead, assessment and treatment of bladder and bowel dysfunction is important.
- ✚ If there are numerous lower urinary tract infections, then a renal sonogram is appropriate

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Treatment**NICE guidelines regarding antibiotic treatment**

Age	Antibiotic Plan
Age < 3 months	<ul style="list-style-type: none"> – IV antibiotics for 2–4 days then – Switch to oral antibiotics if clinically improved
Age > 3 months with upper tract UTI	<ul style="list-style-type: none"> – Oral antibiotic for 7–10 days – IV antibiotics for 2–4 days if vomiting, then oral antibiotics for a total of 10 days
Age > 3 months with lower urinary tract symptoms	<ul style="list-style-type: none"> – Oral antibiotics for 3 days
If a child is on prophylaxis	<ul style="list-style-type: none"> – Change the antibiotic

(Oxford pediatric nephrology)

Empirical antibiotics

Oral antibiotics e.g.	Parenteral antibiotics e.g.
<ul style="list-style-type: none"> – Cotrimoxazole – Amoxicillin – Cefixime – Ciprofloxacin for resistant cases 	<ul style="list-style-type: none"> – Ceftriaxone – Cefotaxime – Ampicillin plus an aminoglycoside e.g. gentamicin

Follow on

- Change antibiotics according to culture and sensitivity
- Urine culture after 1 week to ensure recovery
- Continue antibiotics till urine culture turns sterile, pyuria disappears, afebrile without clinical evidence of UTI
- Urine culture after 3 months → detect recurrence

Supportive care

- Adequate hydration
- Diet, rest and symptomatic treatment e.g. antipyretics
- Admit to hospital sick children (dehydrated, vomiting, ≤1 mo of age)

Prevention: For recurrent urinary tract infections

- Treat risk factor e.g. stones, constipation, voiding dysfunction
- Adequate hydration
- Frequent bladder emptying
- Antibiotic prophylaxis
 - e.g. Low dose cotrimoxazole or nitrofurantion
 - For high risk conditions e.g. neurogenic bladder, and VUR
 - Usually for patients below 3 years
- Probiotic and cranberry juice may have added benefit

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Enuresis

Definitions

- Most children achieve night-time dryness by 5 years of age, when
- bladder volume exceeds nocturnal urine production
- Nocturnal enuresis is involuntary loss of urine at night, in the absence of physical disease, at an age when the child could reasonably be expected to be dry (developmental age of 5 years by consensus)
- Nocturnal enuresis is common, affecting 15–20 % of 5-year-olds, 5 % of 10-year-olds and 1–2 % of 15-year-olds
- Enuresis differs from urinary incontinence that in enuresis the child can control bladder while incontinence means loss of bladder control

Clinical types:

- Primary: the child has never been dry
- Secondary: the child has previously been dry at night for 6 months or more after the age of 5 years;
- Monosymptomatic (uncomplicated): not associated with other urinary tracts symptoms
- Polysymptomatic (complicated) :associated with symptoms suggestive of lower urinary tract dysfunction

Etiology:

Poorly understood

- Developmental disorder: Delay in maturation of bladder control
- Strong genetic component: a family history is found in most children
- Psychological disturbances e.g. emotional deprivation
- Organic causes e.g. mental retardation, urinary tract infections, polyuria as in diabetes mellitus or insipidus.

Management:

1. Proper history taking.
2. Investigations to exclude organic causes.
3. Psychotherapy if emotional factors are present.

General measures

- Adequate daytime fluid intake to develop bladder capacity and reduce evening fluid intake
- Avoid caffeine-based drinks
- Exclude/treat constipation if present
- Consider correction of airway obstruction in heavy snorers
- Pass urine regularly during the daytime and before sleep
- Waking for toileting is used only as short-term management

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Reward systems

- Star charts for dry nights
- Rewards should be given for agreed behavior e.g toileting before sleep,....
- Where these measures alone are unsuccessful, consider the use of an alarm system or drug treatment

Alarm systems

- With alarm system around 50 % of children achieving long-term dryness
- Alarm systems are superior to behavioral techniques and drug therapy
- Use until either 14 consecutive dry nights or 3 months
- Alarms and desmopressin equally effective but alarm has more prolonged effect
- Drawbacks: requires time, motivation, and hard work



Desmopressin

- Has more immediate effect than alarm
- May be used "on important nights only"
- Where successful, treatment should be withdrawn every 3 months to assess response
- Dosage: oral tablets 0.2–0.4 mg or 120–240 micrograms sublingually at bed time
- Keep evening fluid intake below 200 ml and no nighttime drinking
- Stop treatment if no effect within 2 weeks
- Drawbacks: high relapse rate upon stopping
- Can be combined with alarm



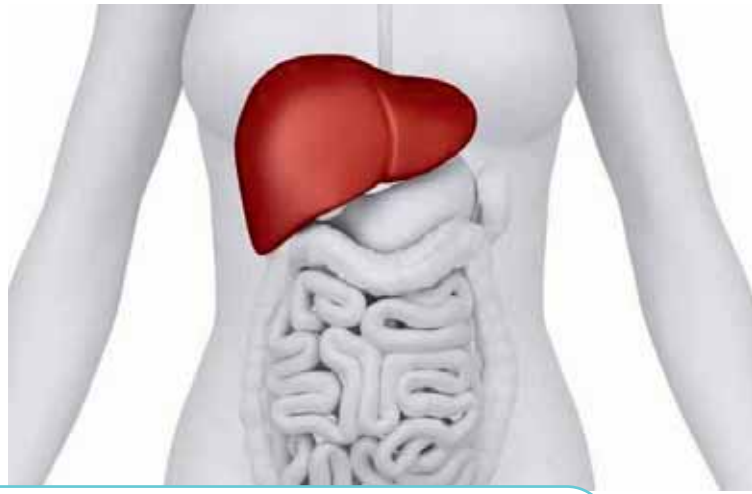
Anticholinergics e.g. Oxybutynin

- May be considered for cases unresponsive to the above therapy
- With or without desmopressin/alarm
- Never combined with tricyclic antidepressants
- Exclude residual urine and/or constipation
- Useful for cases with day time wetting

Tricyclic antidepressants (Imipramine)

- Restricted to those who have not responded to alarm and/or desmopressin
- Have significant adverse-effects ; cardio toxic ,anticholinergic effects
- If used, imipramine should be withdrawn gradually

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الدفعة الـ 14

Causes of vomiting in infants and children

1. Acute infections	2. Metabolic	3. Acute intestinal obstruction
<ul style="list-style-type: none"> - CNS infections - Pulmonary infections - Gastroenteritis - Acute pyelonephritis - Sepsis 	<ul style="list-style-type: none"> - Drug poisoning - Rye's syndrome - Diabetic keto acidosis - Renal failure - Drugs: e.g. aspirin 	<ul style="list-style-type: none"> * Functional: Paralytic ileus * Organic: <ul style="list-style-type: none"> - Intussusception - Volvulus

4. Chronic vomiting

- Over feeding
- Gastro-Esophageal reflux
- Congenital pyloric stenosis
- Inborn errors of metabolism/ adrenal insufficiency
- Psychogenic

Causes of Abdominal pain**i- Acute abdominal pain**

Acute infections	Acute medical conditions	Acute intestinal obstruction
<ul style="list-style-type: none"> - Strept. Pharyngitis (mesenteric adenitis) - Acute hepatitis. - Acute pancreatitis - Acute pyelonephritis - Acute appendicitis. - Acute peritonitis. 	<ul style="list-style-type: none"> - Pneumonia(lower lobe) - Rheumatic fever (peritonitis) - Henoch Schonlein purpura. - Familial mediterranean fever. - Diabetic keto acidosis 	

ii- Chronic (recurrent) abdominal pain

Functional	Organic
<ul style="list-style-type: none"> - Irritable bowel syndrome (in 90%; psychic related) - School phobia 	<ul style="list-style-type: none"> - Intestinal parasites e.g. Giardiasis - Chronic diarrhea (and Malabsorption) - Chronic constipation - Inflammatory bowel disease - H. Pylori infection - Chronic hepatitis - Stones (urinary, biliary)

Q. Causes of constipation?

- Anal fissure
- Spina bifida
- Cretinism
- Intestinal obstruction
- Habitual constipation
- Medications (narcotics)

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Stomatitis

Definition: Inflammation of the oral mucosa

Clinical types

1. Catarrhal stomatitis:

Mild generalized inflammation of the oral mucosa

Causes

- It accompanies acute infections as measles
- Local factors (chemical, traumatic or thermal).

Treatment: may use gentian violet 1 % or local oral anesthetics

2. Herpetic gingivo-stomatitis:

Caused by herpes simplex virus

Clinical picture

- a. Acute onset of fever, anorexia; few days later
- b. Herpetic vesicles appear → minute ulcers
- c. Associations:
 - Pain, excessive salivation
 - Bad mouth odor
 - May be bleeding, swollen gums.



(Nelson 2016)

Treatment

- Care of feeding: cold fluids ± nasogastric tube feeding in severe cases.
- Mouth paint with gentian violet 2% or silver nitrate 2%.
- Antiviral agents as Acyclovir (Zovirax).

3. Thrush stomatitis (Moniliais):

Caused by candida albicans in:

- New born: infected from mothers with genital moniliasis or infected teats
- Malnourished infants due decreased cell mediated immunity
- As a side effect of excess use of antibiotics.

Clinical picture

- Numerous small white flakes
- On the dorsum of tongue, inner side of cheeks & palate.
- In extensive cases a thick white membrane is formed



Prevention

The nipple and areola of the nursing mother should be cleaned before feeding and painted with nystatin ointment in between meals.

Treatment

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4. Gangrenous stomatitis:

- Rare; Seen in severe debilitated children with diseases as measles
- A deep large ulcer on the inn surface of the cheeks that spread slowly by necrosis of adjacent tissues
- It may lead to perforation of the cheek

Treatment: antibiotics plus surgical excision of necrotic areas.

Differential diagnosis of oral ulcers

Common	Criteria
<ul style="list-style-type: none"> ▪ Aphthous (canker sore) 	<ul style="list-style-type: none"> – Painful – Circumscribed lesions – Last 10-14 days – Recurrences ▪ Treatment: benzocaine and topical lidocaine, are effective, as are topical steroids
<ul style="list-style-type: none"> ▪ Traumatic 	<ul style="list-style-type: none"> – Accidents – Chronic cheek biter
<ul style="list-style-type: none"> ▪ Hand, foot, mouth disease 	<ul style="list-style-type: none"> – Painful – Lesions on tongue, anterior oral cavity, hands, and feet
<ul style="list-style-type: none"> ▪ Herpangina 	<ul style="list-style-type: none"> – Painful – Lesions confined to soft palate and oropharynx
<ul style="list-style-type: none"> ▪ Herpetic gingivostomatitis 	<ul style="list-style-type: none"> – Vesicles on mucocutaneous borders – Painful – Febrile
Uncommon	
<ul style="list-style-type: none"> ○ Neutrophil defects 	<ul style="list-style-type: none"> – Agranulocytosis, leukemia, cyclic neutropenia – Painful
<ul style="list-style-type: none"> ○ Systemic lupus erythematosus 	<ul style="list-style-type: none"> – Recurrent – May be painless
<ul style="list-style-type: none"> ○ Behçet syndrome 	<ul style="list-style-type: none"> – Resembles aphthous lesions – Associated with genital ulcers, uveitis
<ul style="list-style-type: none"> ○ Oral Crohn's disease 	<ul style="list-style-type: none"> – Aphthous-like – Painful
<ul style="list-style-type: none"> ○ Stevens-Johnson syndrome 	<ul style="list-style-type: none"> – May be isolated or appear initially in the oral cavity

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Achalasia

Definition

- Esophageal motility disorder characterized by:
 - Failure of relaxation of lower esophageal sphincter (LES)
 - Due to lack of ganglionic cells in the lower esophageal sphincter
 - With subsequent increased lower esophageal sphincter pressure
- Incidence: most cases occur after age of 15 years

Clinical picture

- Dysphagia mainly to liquids rather than to solids that may open LES by weight
- Regurgitation of food
- Cough due to overflow of fluids into trachea (frequent aspiration)
- Recurrent chest infections
- Failure to gain weight in progressive cases

Diagnosis

- Upright chest x ray show air fluid level in dilated esophagus
- Barium swallow **fluoroscopy** shows massive dilatation of the esophagus with tapered lower end



- Esophageal manometry is *diagnostic*; it reveals:
 - ✓ Aperistalsis in the distal esophageal body and
 - ✓ Incomplete or absent LES relaxation, often accompanied by
 - ✓ High pressure LES

Treatment

- Pneumatic dilation is the initial treatment of choice, and does not preclude a future myotomy
- Temporary relief of dysphagia can be offered by calcium channel blockers (nifedipine) and phosphodiesterase inhibitors or endoscopic intra sphincteric injection of botulism toxin
- Heller myotomy: surgical division of muscles at gastroesophageal junction.

Gastro- Esophageal Reflux Disease (GERD)

Definition: Abnormal retrograde of gastric contents into oesophagus due to persistent relaxation of lower oesophageal sphincter (LES)

Incidence: - Mainly in neonates & young infants
- 60% improve with age (resolve by 6 mo-2years).

Clinical picture

A. Uncomplicated cases

1. Vomiting
 - At the end of the feed
 - From the 1st week of life
 - Increase with lying flat
 - May be bile stained.
2. Sandifer syndrome: abnormal head posture and opisthotonus to protect airways.
3. Substernal pain and dysphagia in older child

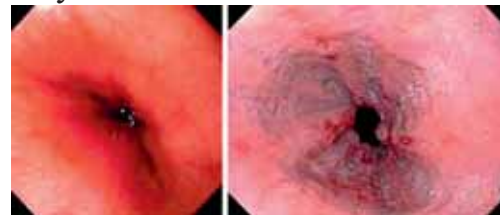
B. Complicated cases

- Oesphagitis → GIT bleeding
- Recurrent aspirations → recurrent aspiration pneumonia
- Chronic cough & chest wheezes
- Growth retardation
- May be sudden infant death syndrome(SIDS) due to laryngospasm and apnea

Investigations

1. Diagnostic:

- **Radiologic**
 - Barium swallow under screen → retrograde of the dye
 - Doesn't assess mucosal inflammation nor the severity of GERD
- **Extended esophageal pH monitoring:** PH < 4 in 5-8% of the monitoring time
- **Endoscopy**
 - Detects low LES pressure by manometry
 - Detect acidic esophageal pH (< 4)
 - Visualize erosive esophagitis and complications such as strictures or Barrett's esophagus



Normal esophagus versus Erosive esophagitis

2. For complications:

Check stool for occult blood

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Treatment

Medical

- Feeding : Thickening feedings with rice or oat cereal (1tablespoon/ounce)
- Position
 - Head up for 30 min after feeding. However, the “infant seat” may worsen reflux by increasing intraabdominal pressure
 - Supine position reduces SIDS but worsen GERD
 - When the infant is awake and observed, prone position and upright carried position can be used to minimize reflux.
- Pharmacotherapy
 - Ameliorate acidity by:
 - Anti-acids
 - Histamin-2 (H2) receptor blockers e.g. Ranitidine
 - Proton pump inhibitors(PPIs) e.g. omeprazole, esomeprazole
 - Prokinetics: controversial and not recommended
 - Domperidone (Risk of cardiac dysrhythmias)
 - Metoclopramide (Risk of tardive dyskinesia)
 - Baclofen ; a centrally acting γ -aminobutyric acid agonist
 - Under research: Metabotropic glutamate receptor 5 antagonists

Avoid methylexanthines → it lowers LES tone

Surgical

Operation

- Fundo plication

Indications

- Failed medical treatment
- Complications. e.g. Growth retardation

Congenital Hypertrophic Pyloric Stenosis

Definition

Progressive hypertrophy of circular muscles fibers of the pylorus with subsequent pyloric narrowing due to ganglionic cells immaturity

Pathogenesis

Progressive vomiting results in:

- Loss of HCL → metabolic alkalosis
- Loss of potassium and chloride → hypokalemia and hypochloremia
- Loss of water and nutrients → dehydration and failure to thrive

Clinical picture

Incidence

- Males (especially first born) affected than females.
- Positive family history may exist.

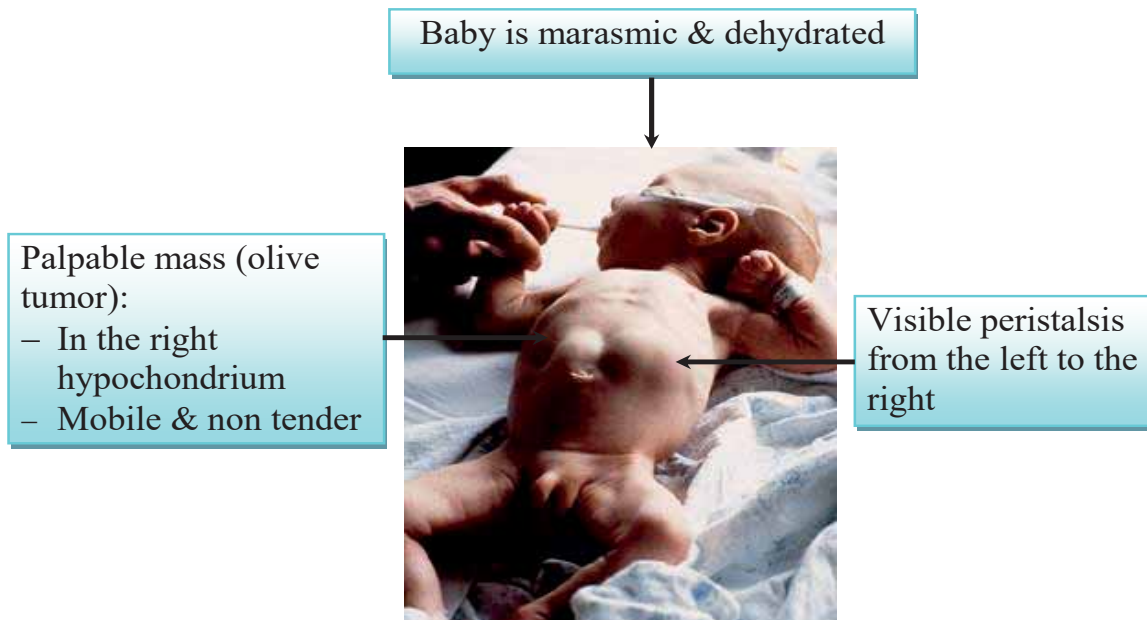
Symptoms

1. Vomiting:

- Occurs shortly after feeding.
- Usually starts after the 2nd – 3th weeks of life (Rarely before or after)
- Initially, non-projectile then projectile
- Non bile stained.
- Baby is often hungry after vomiting.

2. Constipation; passage of small, infrequent stools

Examination



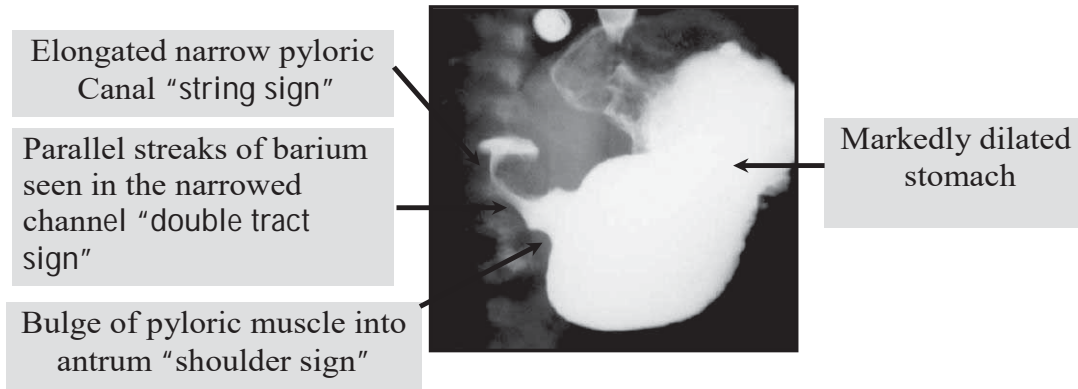
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Differential diagnosis

1. Gastroesophageal reflux disease
2. Adrenal insufficiency (metabolic acidosis and elevated serum potassium and urinary sodium concentration)
3. Inborn errors of metabolism can produce recurrent emesis with alkalosis (urea cycle) or acidosis (organic acidemia) and lethargy, coma, or seizures.
4. Gastro enteritis
5. Other anomalies: pyloric membrane or pyloric duplication, Duodenal stenosis

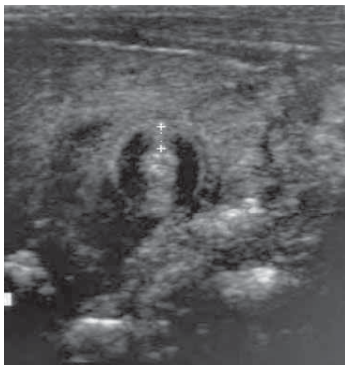
Investigations**1. For diagnosis**

A. Barium meal demonstrates:

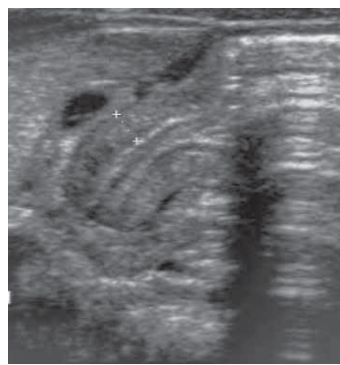


B. **Abdominal ultrasound:** Confirms diagnosis with 95% sensitivity

Criteria for diagnosis:



1. Pyloric thickness 3-4 mm



2. Pyloric length 15-19 mm

3. Pyloric diameter of 10-14 mm

2. For complications

- * Hypochloremic metabolic alkalosis (\uparrow pH, \downarrow CL)
- * Hyponatremia & hypokalemia

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Treatment**1. Surgical:** *Ramstedt's pyloromyotomy*

- Pre-operative → correct electrolytes disturbance and dehydration
- Post-operative → start small feeds → gradually increasing
- Efficiency :100% curative

**2. Medical:** Not efficient, it includes:

- Antispasmodic before feeds
- Small, thick, frequent feeds
- Keep upright for 1 hour after feeding

Congenital Aganglionic Megacolon

(Hirsch sprung Disease)

Definition

- Functional obstruction of the colon due to absence of ganglion cells in bowel wall
- Commonest site: rectosegmoid in 75%

Incidence

- 1 / 5000
- Male: Females = 4: 1 (positive family history may be present).

Clinical picture

1. Presentation may be:

- | | |
|------------------------|---|
| <u>Neonatal (80%):</u> | <ul style="list-style-type: none"> – Delayed passage of meconium beyond 48 hours. – May be acute obstruction |
| <u>In older child:</u> | <ul style="list-style-type: none"> – Chronic constipation and abdominal distension. – Large fecal mass felt in left lower abdomen with empty rectum |

2. Complicated cases:

- Enterocolitis:
 - Infection with clostridia difficile, staph aureus and anaerobes
 - Presented with bloody diarrhea & toxemia
- Intermittent attacks of intestinal obstruction.
- Failure to thrive due to protein losing enteropathy

Investigations

1. Rectal suction biopsy (from narrow segment)

- The gold standard for diagnosing Hirschsprung disease
- Reveals absent ganglia

2. Barium enema:

- Unprepared contrast enema aid in the diagnosis in children older than 1 month of age
- Classic findings: an abrupt narrow transition zone between the normal dilated proximal colon and a smaller caliber obstructed distal aganglionic segment



Treatment

1. Surgical repair.
2. Preparation before surgery:
 - Regular evacuation of rectum.
 - Antibiotics.

Hepatology

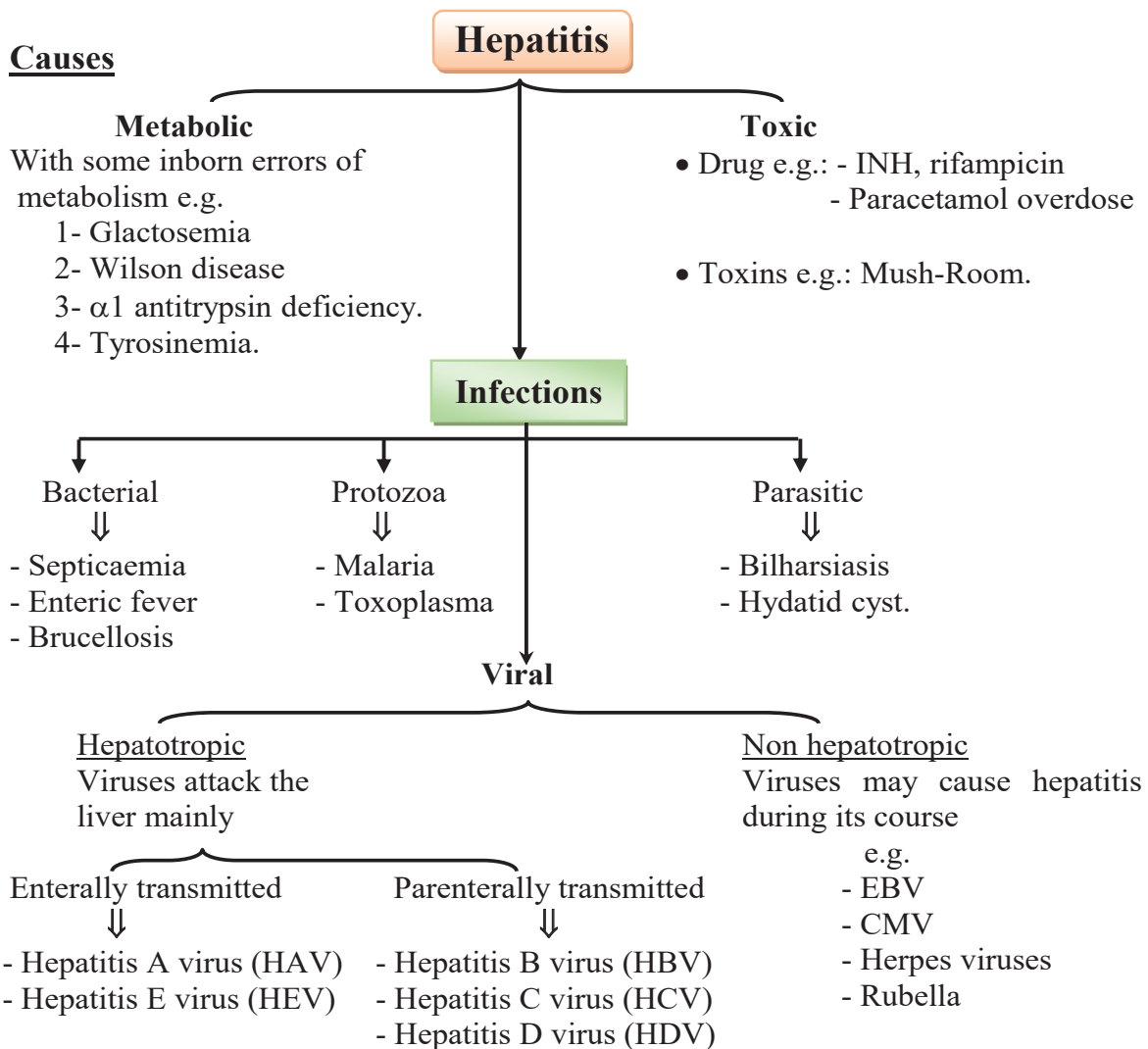
Functions of the liver

- Synthesis of all proteins (except gamma globulin and F VIII)
- Synthesis and excretion of Bile.
- Synthesis and excretion of cholesterol.
- Carbohydrate:
 - Post prandial → convert glucose to glycogen.
 - Fasting → convert glycogen to glucose.
- Detoxication e.g. converts ammonia to urea.

N.B Hepatic enzymes

- ❶ Intra cellular; (Markedly raised in hepatitis):
 - Alanine aminotransferase (ALT); more specific to the liver.
 - Aspartate aminotransferase (AST).
- ❷ Intra canalicular → Alkaline phosphatase, Gamma glutamyl transferase, 5 Nucleotidase ⇒ markedly raised in cholestasis.

Causes



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Acute Viral Hepatitis

Enteral viruses

Include hepatitis A (HAV) and Hepatitis E viruses (HEV)

Criteria

- Excreted only in stool (not in body fluids) so infection occur by faeco-oral route via contaminated water & food.
- None enveloped RNA viruses.
- Incubation period is short (2-6 weeks).
- **Epidemiology:-**
 - Occur in epidemics (highly contagious) or sporadic.
 - Mainly in low socioeconomics
 - HAV is the commonest cause of acute viral hepatitis in school age.
 - HEV is rare in children.
- **Outcome**
 - Complete recovery is the rule; no carrier state nor chronic hepatitis.
 - Fulminant hepatic failure may rarely occur.
 - HEV has high fatality in pregnant women.

Hepatitis A Virus (HAV) (Infective Hepatitis)

HAV is the commonest cause of acute viral hepatitis in school age.

Pathology of acute hepatitis

- Hepatocyte injury is due to cytopathic effects
- Cholestatic jaundice with elevated both direct and indirect bilirubin

Clinical picture of acute hepatitis

- Many cases of viral hepatitis pass asymptomatic.
- Symptomatic cases pass in following phases:

I. Pre-icteric phase (2 – 4 weeks)

- Fever, malaise
- Anorexia, nausea, vomiting
- Abdominal pain
- Diarrhea is frequent in children while constipation predominates in adults

II. Icteric phase (2-4 weeks)

- Improved previous symptoms with appearance of:
 - Jaundice
 - Tender hepatomegaly
 - Dark urine + pale stool



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III. Convalescent phase

- Most patients achieve full recovery
- 2 distinct complications can occur

Complications

1. **Acute liver failure (ALF)**

Incidence: Very rare

- Risk factors: adolescents and adults, immunocompromised patients and those with underlying liver disorders
- In the USA, HAV represents < 0.5% of pediatric-age ALF
- In endemic areas of the world, HAV represents up to 40% of all cases of pediatric ALF

Clinically:

- Deep progressive jaundice
- Bleeding tendency (↓ coagulation factors)
- Generalized edema with ascites
- Disturbed sleep rhythm, tremors, stupor & coma

Fate:

- High mortality rate
- Definitive treatment is liver transplantation.

2. **Prolonged cholestatic syndrome**

- With problematic pruritus and fat malabsorption
- Waxes and wanes over several months

Investigations

A. To prove acute hepatitis:

1. Liver function tests:

- Aminotransferase levels (ALT & AST)
 - Markedly elevated; in thousands
 - The elevation level does not correlate with the extent of hepatocellular necrosis nor to the prognosis
- Serum bilirubin
 - Moderately elevated ;mainly conjugated
 - The first marker to normalize with recovery
- Alkaline phosphatase → mild↑
- Albumin and prothrombin time → usually normal

2. Urine: Dark color due to ↑ cholebilirubin and bile salts

3. Stool: Pale color due to ↓ stercobilinogen.

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In ALF:

1. Aminotransferases rise initially then rapidly decline with rising bilirubin
2. Altered synthetic function:
 - ✓ The most important marker of liver injury and defining severity
 - Abnormal protein synthesis (prolonged prothrombin time, low serum albumin levels)
 - Metabolic disturbances (hypoglycemia, lactic acidosis, hyperammonemia)

B. For the cause → viral serology; HAV markers

Marker	Significance
Anti – HAV (IgM)	Recent HAV infection.
Anti – HAV (IgG)	Previous HAV infection or HAV vaccination; confers long-term protection

Management**General**

- Exclusion of school or child care till one week after clinical jaundice
- Hand washing after defecation or dealing with infected child
- Sterilization of toilet after use

HAV prophylaxis**Indications:**

- Pre exposure for susceptible travelers to HAV endemic countries
- Household post exposure as soon as possible
 - *HAV Ig alone* intramuscular (0.02 mL/kg) if
 - Younger than 12 mo old
 - Vaccine is contraindicated
 - Both *HAV Ig* and the HAV vaccine if
 - Travel is planned in <2 wk
 - Older than 12 mo old
 - Immunocompromised
 - Those with chronic liver disease

HAV vaccine (e.g. *Havrix*):

- Inactivated vaccine, approved for children older than 12 mo
- Dose: 2 doses 6 months apart, IM.

Treatment

- Serial monitoring for signs of ALF and, if ALF is diagnosed, a prompt referral to a transplantation center can be lifesaving (See Later)
- Supportive: bed rest, hydration, high carbohydrate diet, and multivitamins.

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- Avoid hepatotoxic drugs
- Treat complications e.g. antipruritic for prolonged cholestatic syndrome

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Hepatitis E virus

- Share criteria of enteral viruses (see before)
- The epidemic form of what was formerly called non-A, non-B hepatitis.
- Transmission is fecal–oral (often waterborne)
- The prevalence appears to be increasing, so that it is postulated to be the most common cause of acute hepatitis and jaundice in the world

Clinically

- The clinical illness associated with HEV infection is similar to that of HAV but Often more severe especially in pregnant women, in whom it causes ALF with a high fatality incidence
- Tends to affect older patients, with a peak age between 15 and 34 yr

Prevention

- A recombinant hepatitis E vaccine is highly effective in adults

Diagnosis

- Antibodies to HEV particles; IgM and IgG assays are available to distinguish between acute and resolved infections

Parenteral viruses

Include Hepatitis B virus (HBV), Hepatitis C virus (HCV) and Hepatitis D virus (HDV)

Criteria:

Acute hepatitis due to parenteral viruses occur sporadically **not** in epidemics

	HBV	HCV	HDV (Delta virus)
Nature	Enveloped DNA virus.	Non enveloped RNA virus.	Non enveloped RNA virus → need HBV coat to be infective (defective virus; dependent on HBs Ag).
Risk factors	<ul style="list-style-type: none"> ▪ Perinatal exposure to an infected mother (The most important risk factor for acquisition of HBV in children) ▪ Parenteral via: <ul style="list-style-type: none"> – Post transfusion ; via contaminated blood products (The most important risk factor for acquisition of HCV) – Hemodialysis patients – Drug abusers ▪ Sexual ▪ No risk factors identified in approximately 40% of cases 		
Incubation period	2-6 months	2-4 months	

Pathology of acute hepatitis

- Hepatocyte injury can be due to:
 - Cytopathic effects (by all except HBV)
 - Immune mediated cell lysis (by HBV & HCV)
- Cholestatic jaundice with elevated both direct and indirect bilirubin
- In perinatal HBV infection : markers of infection and antigenemia appear 1-3 mo after birth

Clinical picture of acute hepatitis

- Many cases of acute hepatitis pass *asymptomatic*
- Symptomatic cases are similar to that of **HAV**
- Acute HCV infection tends to be mild and insidious in onset unlike HBV
- Extrahepatic manifestations due to circulating immune complexes; mainly in HBV & HCV:
 - Serum sickness like prodrome marked by arthralgia or skin lesions e.g. urticarial, purpuric, macular, or maculopapular rashes
 - Aplastic anemia
 - Glomerulonephritis
 - Vasculitis

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Complications

1. Chronic carrier state
2. Chronic hepatitis

Risk:

- Risk of chronic HBV infection is 90% in children younger than 1 yr; 30% for those 1-5 yr and 2% for adults
- HCV is the commonest cause ever of chronic viral hepatitis

Complications

- Cirrhosis & liver cell failure.
 - Hepatocellular Carcinoma
3. Acute Liver Failure (ALF); risk increases when there is coinfection or superinfection with HDV and in an immunosuppressed host
 4. Reactivation of chronic infection has been reported in immunosuppressed children

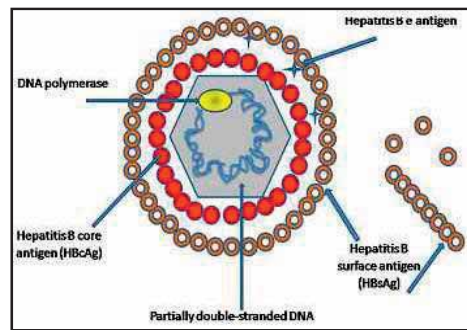
Investigations

I. To prove acute hepatitis: As in HAV

II. For Etiology: Viral Markers



1. For HBV



Marker	Significance
▪ HBs Ag	<ul style="list-style-type: none"> – Acute infection; its rise closely coincides with the onset of symptoms – If persist > 6 months → indicate chronic hepatitis
▪ Anti HBc Ag IgM	<ul style="list-style-type: none"> – Acute infection; Reliable single marker later in the acute phase as HBs Ag fall before the symptoms disappear
▪ Hbe Ag	<ul style="list-style-type: none"> – Acute infection ; a marker of active viral replication and usually correlates with HBV DNA levels – HBe Ag positive mothers put very high risk of perinatal transmission to their babies
▪ Anti HBc Ag IgG	<ul style="list-style-type: none"> – Infection; recent <u>or</u> chronic
▪ Anti HBs Ag	<ul style="list-style-type: none"> – If present alone, it indicate previous vaccination. – If present with anti-HBc Ag → resolved infections.

N.B. HBc – Ag is present only inside the hepatocytes.

Hbe – Ag is not structural antigen but it is produced by self-cleavage of the core antigen

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2. For HCV and HDV

- Detect specific RNA by PCR.
- Detect specific antibodies.

N.B: Children born to HCV-infected women → test for qualitative PCR in infancy and anti-HCV after 12-18 mo of age

Prevention

1. Blood donation screening

2. HBV immunization

Combined: Both vaccine and immunoglobulin

A. Post exposure prophylaxis for infant born to HBs Ag + ve mothers

- HBV immunoglobulin 0.5 ml IM, within 12 hr after birth plus the first dose of HBV vaccine (which is given as 0, 1, 6)
- Protective value of this regime is > 95%
- Follow up: Post vaccination testing for HBsAg and anti-HBs should be done at 9-18 mo:

If {

- Positive for anti-HBs → The child is immune
- Positive for HBs Ag only → The child is infected
- Negative for both HBsAg and anti-HBs → Repeat the vaccine

B. Post exposure in older child:

HBV immunoglobulin: 0.06 ml/kg within 24 hrs plus HBV vaccine which given as 0, 1, 6

Active

- HBV vaccine: (Recombivax HB and Engerix-B)
- Nature: Recombinant DNA vaccine.
- Time: 3 doses, IM at 0, 1, 6 months

Treatment

- As for HAV; Treatment of acute infection is largely supportive.
- Close monitoring for liver failure and extrahepatic morbidities is key
- **Acute liver failure** management include:
 - Referral to PICU in a center expert in liver transplant
 - Monitor vitals , conscious state and hepatic / renal chemistry
 - Fluid ,glucose, ammonia and electrolytes monitoring and correction especially for hypophosphatemia (high phosphate is a bad sign)
 - Restrict or forbid proteins initially
 - Gastriprotection :proton pump inhibitors
 - Oral antibiotics (e.g. Neomycin) and Lactulose to sterilize the colon
 - Frequent enema preferably with lactulose
 - Correct coagulopathy by vit K, fresh frozen plasma or factor VIIa
 - In advanced cases with coma: Hepatic dialysis/transplantation

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Chronic Hepatitis

Definition: An inflammatory process of the liver lasting longer than 6 months.

Recently → continuing hepatic inflammatory process manifested with severe liver disease **or** features of chronicity (shorter time can be employed)

Chronic persistent hepatitis	Chronic active hepatitis
Causes Viral → HBV, HCV	<ul style="list-style-type: none"> ▪ Auto immune → the commonest ▪ Viral → HBV, HCV, Delta virus. ▪ Metabolic → e.g. Wilson disease.
Pathology <ul style="list-style-type: none"> - Inflammation limited to the portal zone - Little or no fibrosis. - No cirrhosis. 	<ul style="list-style-type: none"> - Erosions of the limiting plate. - Piecemeal necrosis of hepatocytes. - If severe → bridging necrosis → fibrous septa
Clinical picture <ul style="list-style-type: none"> - Asymptomatic - May be non-specific: malaise, anorexia - May be tender hepatomegaly. 	<ol style="list-style-type: none"> 1. Most cases have: <ul style="list-style-type: none"> - Hepatosplenomegaly (HSM) - Liver cell failure (LCF) 2. In auto immune; type there may be also: <ul style="list-style-type: none"> - Iridocyclitis - Thyroiditis - Vasculitis → nephritis - Serositis → arthritis , pleurisy - Immune hemolytic anemia - Clubbing
Complications Very uncommon	Common: -Cirrhosis→ portal hypertension -Fulminate hepatic failure.
Investigations <ol style="list-style-type: none"> 1. Is it hepatitis? Yes. <ul style="list-style-type: none"> - ALT & AST → mild increase. - Bilirubin → No or slight increase. 2. Is there liver decompensation? No <ul style="list-style-type: none"> - Albumin → Normal. - Prothrombine time → normal. 3. What is the cause? <ul style="list-style-type: none"> - HBV & HCV markers. 	Yes → High (not alkaline phosphatase) → High. (2-10 mg/dl – mainly direct). Yes → Low → Prolonged 1- Viral markers. 2- For auto immunity: <ul style="list-style-type: none"> - Anti nuclear antibody (ANA). - Anti – smooth muscle antibody. - Anti liver kidney microsomal antibody - Anti soluble liver antigen antibody. - Elevated γ-globulin levels 3- Metabolic assay.
- Liver biopsy → diagnostic	

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Treatment

1. Supportive → As in acute hepatitis

2. Follow up → Clinical (for signs of decompensation) **and** laboratory.

3. Specific:

Auto immune hepatitis:

- Steroids 1-2 mg / kg /day till ALT & AST less than twice high normal
- Then taper slowly over 2-4 months to reach maintenance dose of 0.1 – 0.3 mg/kg/day



If steroids were poorly effective or have side effects



- Azathioprine is added with frequent monitoring for bone marrow suppression
- Measurement of thiopurine methyltransferase activity before azathioprine therapy is a predictive of myelotoxicity

Post viral:

HBV

- Treatment is only indicated for patients in *the immune active* form of the disease, as evidenced by elevated ALT and/or AST, who have fibrosis on liver biopsy
- Medications
 - Interferon-α2b
 - Peginterferon-α2
 - Lamivudine
 - Adefovir

HCV

- Medications approved by the FDA for use in children older than 3 yr of age with HCV hepatitis
 - Interferon-α2b
 - Peginterferon
 - Ribavirin
 - New therapies: direct-acting antivirals: Sofosbuvir and Simeprevir

4. Treat complications e.g.

- Cirrhosis and fulminant hepatic failure → liver transplant

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Reye's syndrome

Definition

Acute mitochondrial encephalopathy with hepatic fatty degeneration

Clinical picture

- Precipitated in a *genetically susceptible* person by the interaction of a viral infection (influenza, varicella) and salicylate and or antiemetic use
- Manifestations appear 5-7 days following viral infection



- Acute hepatomegaly
- The patient remains anicteric



- Acute rise of the intra cranial tension:
 - Severe profound vomiting
 - Delirium and stupor
 - Generalized fits → coma
 - Eventual herniation is the main cause of death

Diagnosis



- Coagulopathy and elevated aminotransferases, and ammonia and hypoglycemia
- Liver biopsy → Fatty infiltration and mitochondrial damage



- Cranial CT → Brain edema
- CSF is normal but with raised pressure (be cautious with lumbar puncture)

Differential diagnosis

Reye like conditions with some inborn errors of metabolism e.g. Fatty acid oxidation defects and valproate toxicity

Treatment

Largely supportive

- Supportive care for acute liver failure
- Coma care and reduction of raised intracranial tension

Wilson diseases

(Hepato lenticular degeneration)

AR defect in ceruloplasmin (Copper carrying protein) → Copper accumulate in:

▪ Liver	Forms of hepatic disease include <ul style="list-style-type: none"> – Asymptomatic hepatomegaly (± splenomegaly) – Subacute or chronic hepatitis – Acute hepatic failure – Cryptogenic cirrhosis, portal hypertension
▪ Basal ganglia	<ul style="list-style-type: none"> – Intention tremor, dysarthria, rigid dystonia, chorea – Deterioration in school performance – Behavioral changes/ Psychiatric manifestations
▪ Anemia	– Coombs-negative hemolytic anemia
▪ Cornea	– Kayser Flisher ring <i>(absent in young patients)</i>
▪ Renal tubules	– Tubular defects (Fanconi like)



Diagnostic triad

- ↓ Serum ceruloplasmin (< 20 mg/dL).
- ↑ Urinary copper excretion after loading dose of D-penicillamine
- Liver biopsy → hepatic copper accumulation.

Screening

Family members of patients with proven cases require screening for presymptomatic Wilson disease. Screening include determination of the serum ceruloplasmin level and urinary copper excretion

Treatment

- Restrict dietary copper intake to <1 mg/day
- Copper chelating agent
 - D-penicillamine 20 mg/kg/day (penicillamine is an antimetabolite of vitamin B6, additional amounts of this vitamin are necessary)
 - Alternative : triethylene tetramine dihydrochloride (trientine)
- Adjuvant therapy: Oral zinc
- Liver transplant

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Liver Cirrhosis

Definition: Chronic liver disease with triad of:

- Hepatocytes necrosis.
- Regeneration nodules.
- Lost hepatic architecture.

Causes:

- Post hepatic.
- Metabolic: e.g. Wilson & hemochromatosis.
- Biliary: 1ry or 2ry to bile flow obstruction.
- Chronic hepatic congestion: cardiac cirrhosis.

Clinical picture

- **Compensated** : Clinical picture of the cause.
- **Decompensated: Features of liver cell failure**
 - 1- Jaundice.
 - 2- Bleeding tendency:
 - Skin bruises.
 - GIT bleeding → Hematemesis & melena.
 - 3- Ascites & generalized edema.
 - 4- Hepatic encephalopathy:
 - Due to increased ammonia and neurotoxins (false neurotransmitters).
 - Manifested by: Disturbed sleep rhythm, flapping tremor, coma.
 - 5- Hepato-renal syndrome: Functional renal failure in patients with end stage liver disease due to intense renal vasoconstriction with systemic vasodilatation → renal hypoperfusion → pre renal failure
 - 6- Hepato pulmonary syndrome: - Intrapulmonary vascular dilatation → right to left shunting of blood → hypoxemia, dyspnea, cyanosis & clubbing.
 - 7- Others:
 - Feotor hepaticus.
 - Palmar erythema.
 - Spider nevi.
 - Muscle wasting.

Diagnosis

- 1- To prove cirrhosis:
 - Abdominal ultrasound & MRI.
 - Liver Biopsy → diagnostic (but avoided if decompensated)
- 2- For the cause: e.g. viral markers.
- 3- For complications:
 - Liver functions tests → bilirubin, prothrombin time, albumin.
 - Portal hypertension → **see later**.

Treatment

- 1- Supportive
 - Carbohydrates and vitamins rich diet
 - Low salt diet (for cases with edema)
 - Limit protein (for cases prone to encephalopathy)
- 2- Ant fibrotic: Colchicine.
- 3- Treatment of complications.
- 4- Liver transplant.

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Ascites

Definition: Accumulation of fluid in peritoneal cavity.

Transudate	Exudate	Bloody	Chylous
<ul style="list-style-type: none"> - Clear - ↓proteins (<3gm/dl) - ↓ Cells - ↓Specific gravity. - No organisms. 	<ul style="list-style-type: none"> - Turbid - > 3 gm / dl - ↑ cells (PMNL) - ↑ (> 1018) - may be organisms. 	Bloody with RBCs on mic. ex.	Milky white
Causes: 1. Causes of generalized edema; cardiac, hepatic, renal 2. poly serositis	<ul style="list-style-type: none"> - Septic peritonitis - T.B. peritonitis - <u>Non microbial</u>: <ul style="list-style-type: none"> • systemic lupus • Metastasis • B-cell lymphoma 	<ul style="list-style-type: none"> - Trauma - Tumors - Bleeding disorders - Acute hemorrhagic pancreatitis 	Rupture thoracic duct due to trauma. Or obstruction.

Other causes: Bilious, urinary

Clinical diagnosis: see *SHOTS* clinical examination

Treatment of hepatic ascites:

- 1- Liver support (vitamins, avoids hepato toxic drugs, high carbohydrate diet).
- 2- Low salt and protein diet.
- 3- Diuretic: Aldactone.
- 4- Albumin or plasma infusion.
- 5- Therapeutic paracentesis provided:
 - Tense ascites.
 - Prothrombin concentration > 40%.
 - Bilirubin < 10 mg/dl.
 - Platelets > 40.000/mm³.
 - Creatinine < 3 mg/dl.
 - Aspirated volume not more than 20ml/kg/setting



Portal Hypertension

Definition: an elevation of portal pressure $>10-12$ mm Hg (normal < 7 mmHg)

Causes:

Portal hypertension can result from obstruction to portal blood flow anywhere along the course of the portal venous system

i. Extra hepatic portal hypertension:

- Portal or splenic vein thrombosis due to:
 - Umbilical infection.
 - Neonatal sepsis.
 - Hypercoagulable states e.g. protein S & protein C deficiency.
 - Intra-abdominal infections
- Inferior vena cava obstruction with e.g. constrictive pericarditis/thrombosis
- Congestive heart failure/tricuspid regurge

ii. Intra hepatic portal hypertension:

1. Pre sinusoidal	→	- Chronic hepatitis. - Schistosomiasis. - Portal tract infiltrations
2. Sinusoidal	→	- Cirrhosis (the commonest cause) - Veno oculsive disease
3. Post sinusoidal	→	- Budd-Chiari syndrome

(Nelson textbook of pediatrics 2016)

Clinical picture

- Opened collaterals
 - Esophageal varices → hematemesis & melena (the commonest presentation)
 - Caput medusa
 - Hemorrhoids
 - Venous hum
- Splenomegaly (the next most common presentation)
- Ascites
- Liver is
 - Shrunken in cirrhosis.
 - Enlarged tender in post sinusoidal causes
 - Normal in prehepatic causes.

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Investigations

- 1- Abdominal ultrasound → for liver, spleen, ascites.
- 2- Measure portal vein pressure by ultrasound Doppler.
- 3- Upper GIT endoscopy for esophageal varices
- 4- Search for the cause.

Treatment**i. Emergency treatment (Control bleeding esophageal varices):**

- ABC
- Take blood sample for investigation & ask for blood.
- Order fresh blood transfusion
- Fluid resuscitation followed by replacement of red blood cells
- Correct coagulopathy by:
 - Vitamin K I.V
 - Fresh frozen plasma or platelets
 - Place nasogastric tube → to monitor ongoing bleeding.
 - H2-receptor blocker or proton pump inhibitor should be given intravenously → reduce the risk of bleeding from gastric erosions

In most patients, particularly those with extrahepatic portal hypertension and with normal hepatic synthetic function, bleeding usually stops spontaneously

**With continued bleeding**

- Vasopression or Octreotide I.V infusion → ↓ splanchnic flow.
- Nitroglycerine skin patch decrease portal pressure and can ameliorate some of its untoward effects of vasopressin
- Endoscopic sclerotherapy with ethanol amine or much better band ligation of varices.

**With continued bleeding**

- Sengstaken – Blackmore tube → mechanical compression of esophageal & gastric varices (this device is rarely used now)

ii. Prophylactic (Prevent subsequent bleeding):

- Propranolol → ↓ portal pressure
- Porto-systemic Shunt operation
- Trans jugular intrahepatic porto systemic shunt (TIPS) by an interventional radiologist (problem→may precipitate hepatic encephalopathy and is prone to thrombosis).

iii. Orthotopic liver transplantation

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Gastrointestinal Bleeding

Causes

- **Upper GIT bleeding:** Bleeding from above the ligament of Treitz:
 - a. Esophageal:
 - GERD
 - Varices
 - Tumors.
 - b. Gastric ulcers.
 - c. Duodenal ulcers.
- **Lower GIT bleeding:** Bleeding below the ligament of Treitz:
 - Inflammatory bowel disease.
 - Intestinal obstruction (intussusception & volvulus)
 - Meckel's diverticulum.
 - Gastroenteritis.
 - Anal fissure.
- **Hemorrhagic blood disease:**
Result in either upper or lower GIT bleeding e.g. hemophilia, purpura, DIC.

Management

1. Emergency treatment as (See bleeding esophageal varices).
2. Search for the cause:
 - a. History of: - Bleeding disorder// Liver disease// Gastroenteritis.
 - b. Examination:
 - Skin for → Signs of chronic liver disease.
 - Signs of coagulopathy (e.g. purpura & Bruises)
 - Abdominal → Hepatosplenomegaly (in chronic liver disease & leukemia)
 - Distension (intestinal obstruction)
 - P/R examination → For perianal ulcers & polyps.
 - c- Investigations:
 - Rule out hemorrhagic blood diseases by → CBC
 - Coagulation profile
 - Liver function tests
 - Abdominal X-ray and ultrasound → for obstructions & organomegaly.
 - Stool analysis → For gastro enteritis & enterocolitis.
 - Endoscopy → for varices, ulcers, polyps.

Treatment: of the cause

- **Medical** e.g. for Hemorrhagic blood diseases, Gastro Enteritis
- **Interventional / Surgical** e.g. for Varices, Polyps

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Veno Occlusive Disease(VOD)



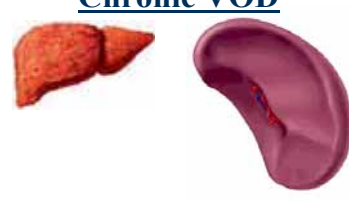
(Sinusoidal obstruction syndrome)

The most common cause of hepatic vein obstruction in children

Definition : Intrahepatic obstruction of hepatic veins.

Causes : After total body irradiation with or without cytotoxic drug
May be toxic injury by herbal teas or drugs

Clinical picture

<u>Acute VOD</u>	<u>Subacute VOD</u>	<u>Chronic VOD</u>
		
<ul style="list-style-type: none"> - Portal hypertension - Hepatomegaly. - No splenomegaly. 	<ul style="list-style-type: none"> - Portal hypertension - Hepatomegaly - Splenomegaly 	<ul style="list-style-type: none"> - Portal hypertension - Cirrhotic liver - Huge Splenomegaly

Diagnosis

- 1- As for portal hypertension
- 2- Liver biopsy → diagnostic.

Treatment

- Supportive
- In severe cases: liver transplantation

Budd Chiari Syndrome

Definition: Obstruction of the main hepatic veins.

Causes

- Hypercoagulable states e.g. Polycythemia ,
- Can complicate hepatic or metastatic neoplasms, collagen vascular disease, infection, and trauma

Clinical picture

Acute stage

- Acute hepatomegaly
- Acute abdominal pain & vomiting.
- Acute ascites

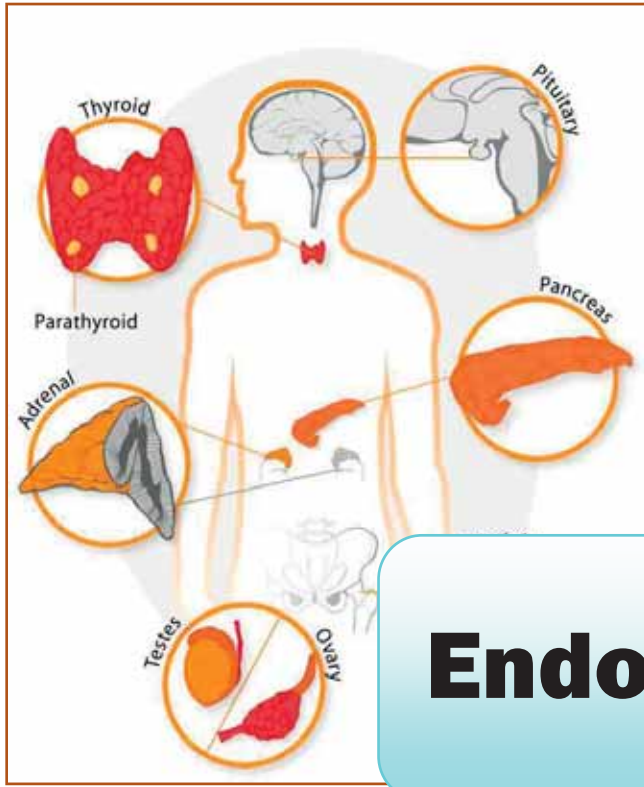
Chronic stage.

- Hepatomegaly.
- Portal hypertension.

Treatment

- Supportive
- In severe cases: liver transplantation

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Endocrinology

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الدفعة ال14

Hypopituitarism

Definition

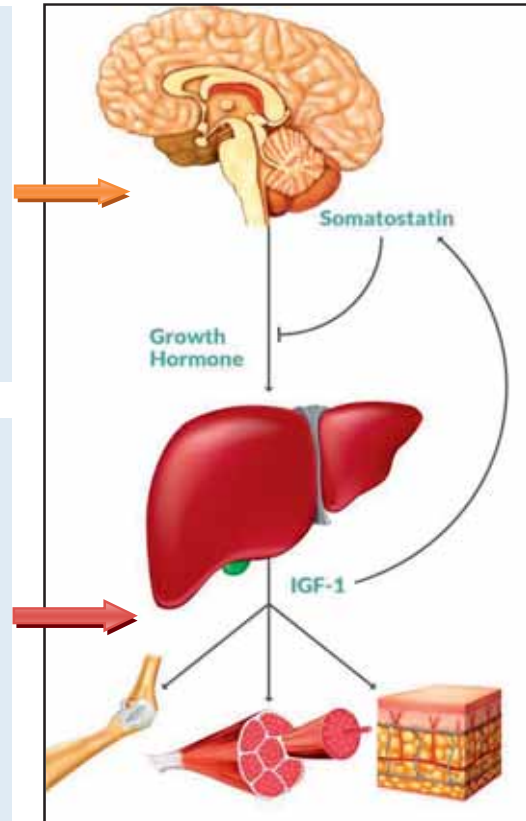
Underproduction of growth hormone (GH) alone or in combination with deficiencies of other pituitary hormones

Physiology of growth hormone

- GH is secreted from the anterior pituitary in bursts (i.e. pulsatile pattern) under control of hypothalamic GH releasing hormone (GH. rH)
- GH release is:
 - Stimulated by sleep, exercise and hypoglycemia
 - Inhibited by somatostatin

Actions

- Anabolic hormone especially on long bones and muscles
- Action is mediated by Insulin Growth Factor 1 produced by the liver:
 - Increase protein synthesis
 - Anti-insulin effect → lipolysis & ↑ blood glucose



Causes

i. Isolated growth hormone deficiency:

A. Genetic: due to

- Mutation of growth hormone genes; AR, AD or XLR.
- End organ resistance:
 - Defective GH receptors e.g. Laron syndrome
 - Post receptor GH insensitivity e.g. abnormal IGF gene or receptor

B. Acquired:

- Idiopathic (The most common).
- Post cranial irradiation (e.g. for leukemia).

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ii- Multiple pituitary hormones deficiency:

A. Genetic:

- Due to mutations of multiple pituitary hormones genes e.g. PROP1
- Associations: May be optic nerve dysplasia (septo optic dysplasia).

B. Congenital:

- Pituitary aplasia or hypoplasia.
- Association: May be mid facial anomalies e.g cleft palate, solitary maxillary central incisor

C. Acquired any lesion at hypothalamo- hypophyseal region:

- Tumors e.g. Craniopharyngioma
- Trauma
- Infiltration e.g. histiocytosis

Clinical picture

1. At birth:

- Normal size (near normal weight and height)
- Micropenis is a diagnostic clue.>
- May be neonatal emergency as apnea, cyanosis, hypoglycemia
- May be mid facial anomalies e.g. cleft lip & palate



2. Later on:

Severe growth failure

- Proportionate short stature
- Height below the 1st percentile for age and sex
or height >2 SD below sex adjusted Mid-parent height
- Growth velocity $< 5\text{cm/year}$
- Appear by the end of the 2nd year



Normal intelligence

Childish facies

- Small face, nose & mandible
- Prominent forehead & depressed nasal bridge
- Wide anterior fontanel & fine hair
- Delayed teething

- Micropenis in childhood; normal for body size in adults
- Hypoglycemia: in infants and children; fasting symptoms in some adults

3. May be features of:

- Septo optic dysplasia : nystagmus & visual impairment in infancy
- Mid facial anomalies e.g. cleft lip / palate, solitary maxillary central incisor
- Increased intra cranial tension (in destructive lesions)
- Associated hormonal deficiency e.g. hypothyroidism, diabetes insipidus



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Investigations

1. Screen for GH deficiency

- Low serum levels of IGF-1 and the GH-dependent IGF-Binding Protein 3 matched to normal values for skeletal age rather than chronological age
- Normal values IGF-1 and IGF-Binding Protein 3 indicates GH deficiency unlikely

2. Confirm GH deficiency

- Measure peak levels of GH after provocative agents; insulin, clonidine, or arginine or glucagon:
 - Normal peak levels of GH $\Rightarrow > 10 \text{ ng/ml}$
 - Low peak levels of GH ($<10 \text{ ng/mL}$) \Rightarrow GH deficiency
 - To confirm diagnosis 2 provocative tests should be done
- In prepubertal children: A 3 days of estrogen priming should be used before GH testing to achieve greater diagnostic specificity.

3. For associated deficiencies:

- Measure other anterior pituitary hormones.

4. For the cause:

- Skull CT & MRI for pituitary tumors, aplasia or hypoplasia
- TRH stimulation test (differentiate between hypothalamic and pituitary causes)
- Random prolactin level: high in hypothalamic defects

5. For effect: Radiograph for delayed bone age

Treatment

1. Recombinant GH:

- Dose: 0.18-0.3 mg/kg/week, divided into 6-7 daily subcutaneous injections should be used as soon as GH deficiency is diagnosed
- Criteria to stop therapy:
 - A decision by the patient that he or she is tall enough
 - A growth rate $<1 \text{ inch/yr}$
 - And a bone age $>14 \text{ yr}$ in girls and $>16 \text{ yr}$ in boys
- Concurrent treatment with a gonadotropin-releasing hormone (GnRH) agonist to interrupt puberty will delay epiphyseal fusion and prolong growth
- Side effects of GH therapy:
 - A 6-fold increase in the risk for type 2 diabetes
 - Pseudotumor cerebri
 - Slipped femoral epiphysis

2. Recombinant IGF-1 for end organ unresponsiveness (e.g. Laron syndrome)

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3. Treatment of other hormonal deficiency

4. For infants with micropenis:

One or two a 3-mo courses of monthly intramuscular injections of 25 mg of testosterone enanthate can bring the penis to normal size

Puberty

Definition

- It is a period of growth lasting 5 years, consisting of 3 stages and includes physical, sexual & psychological changes.
- Onset Girls: 8-13 years, Boys: 9-14 years
- Sequence :

Girls	Boys
<ul style="list-style-type: none"> - Breast development - Pubic hair - External genitalia maturation - Feminine habitus - Axillary hair - Oil secretion and acne - Menstruation 	<ul style="list-style-type: none"> - Testicular growth - Pubic hair - Penis and scrotal growth - Increased muscle bulk - Body hair (beard, axillary) - Oil secretion and acne - First seminal discharge.

Thyroid Gland

Thyroid gland secrete

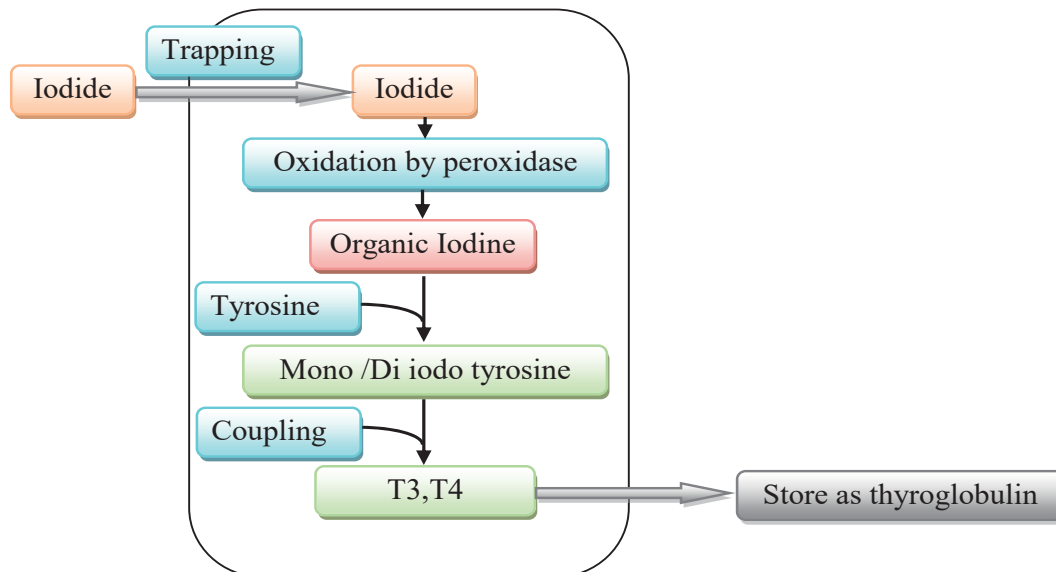
- Thyroid hormones:
 - Thyroxine (T4)
 - Triiodothyronine (T3) ; more potent than T4
- Calcitonin (which deposit calcium salts in bone).

Functions of thyroid hormones

- 1- Normal maturation of the growing brain in the 1st year of life.
- 2- Normal skeletal growth.
- 3- Oxidative metabolism & energy production in all cells

Thyroid hormones synthesis

- Iodide transport (Trapping).
- Iodide is oxidized to iodine by thyroid *peroxidase enzyme* (organification).
- Iodination of tyrosine to form Mono & Di iodo tyrosine.
- Coupling of:
 - 2 Di iodotyrosine → T4
 - Monoiodotyrosine & Di iodotyrosine → T3
- T3 & T4 are stored in thyroid gland as colloid (thyroglobulin).
- Only 20% of circulating T3 is produced by thyroid while 80% is produced by peripheral conversion of T4 by deiodinase



Control of thyroid function:

- Thyroid is regulated by pituitary thyroid stimulating hormone (TSH) in a feedback mechanism.
- TSH synthesis & release is controlled by hypothalamic TSH releasing hormone (TRH).

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Congenital hypothyroidism

Causes

A. Primary hypothyroidism:

1. Thyroid dysgenesis:

- The commonest cause (85%).
- Aplasia, hypoplasia or ectopic gland (may be lingual, sublingual or subhyoid).



2. Defective thyroid hormone synthesis (Dyshormonogenesis):

- The second common (15%)
- Autosomal recessive disorders
- Associated with goiter.
 - Examples:- Iodide transport defect.
 - Organification defect: defective thyroid peroxidase enzyme

3. Transient hypothyroidism:

- Trans placental passage of maternal anti thyroid drugs
- Neonatal iodine containing antiseptics

4. Maternal iodine deficiency → Endemic goiter

5. End organ unresponsiveness to: - TSH.

- T3 & T4 (Pseudohypothyroidism).

B. Secondary hypothyroidism:

Due to TSH deficiency either: - Isolated or.

- With multiple pituitary deficiencies.

C. Tertiary hypothyroidism:

Due to TSH releasing hormone deficiency

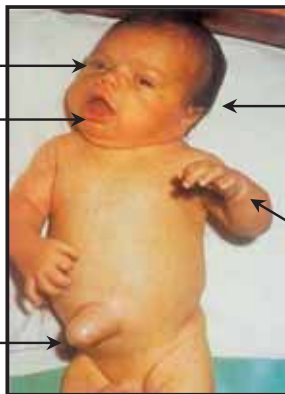
Incidence: 1:4000; Female: male = 2:1.

Clinical picture

A. In neonatal period: there is may be

- Prolonged physiologic jaundice
- Poor feeding → choking spells during feeding.
- Subnormal temperature

- Noisy breathing due to large tongue.
- Abdomen : constipation & umbilical hernia



- Lethargy; cry little, sleep much.
- Widely open posterior and anterior fontanelles (*Good initial clue*)

- May be heavier at Birth
- May be Limbs and genital edema

N.B: Most infants with congenital hypothyroidism are asymptomatic (due to Trans placental maternal thyroxin), so neonatal screening is mandatory

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B. Full picture (by end of the 1st year): (cretinism)

- * Delayed growth \Rightarrow Short stature with persistent infantile proportions
- * Delayed mental milestones
- * Delayed motor milestones
- * Physical features may include:

**Head**

- Coarse, brittle hair with low anterior hair line
- Delayed closure of anterior fontanel
- Eyes are puffy, narrow palpebral fissure
- Broad nose & depressed bridge
- Delayed teething
- Thick large protruding tongue

**Neck**

- Short neck with supraclavicular pad of fat
- Thyroid is enlarged in:
 - Endemic goiter.
 - Dyshormonogenesis
 - Pseudohypothyroidism
- Hoarse cry

Cardiac

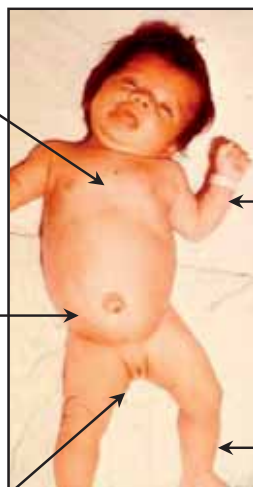
- Bradycardia
- Pericardial effusion
- Cardiomegaly

Abdomen

- Protuberant
- Umbilical hernia
- Constipation

Genitalia

- Delayed maturation
- Rarely precocious puberty

**Limbs**

- Short broad hands
- Generalized hypotonia
- Occasional reversible generalized pseudohypertrophy most prominent in calf (*Kocher Debre Semelaigne Syndrome*)

Skin

- Cold & pale (resistant anemia)
- Dry (\uparrow myxematous tissue)
- May be yellow (\uparrow carotene)

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Investigations

1. Confirm diagnosis of hypothyroidism

- Low serum free T_4 (*In hypothyroidism there's compensatory increase in peripheral conversion of T_4 to T_3 ; so measuring of T_3 may be misleading*)
- Serum TSH
 - High in primary hypothyroidism
 - Low in secondary and tertiary hypothyroidism.
- In pseudohypothyroidism T_4 , T_3 and TSH all are high

2. For effect

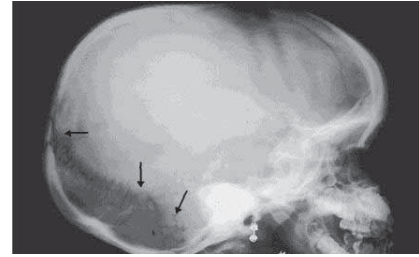
Radiograph findings



(a)



(b)



(c)

- Delayed bone age:
 - At birth → absent distal femoral epiphysis (in plane knee radiograph) in 60% of cases (a)
 - Later → delayed appearance of ossific centers (by wrist x-ray)
- Epiphyseal dysgenesis: multiple foci of ossification in heads of femur & humerus (b)
- Skull X-ray → Intrasutural (Wormian) bones (c) and large fontanelles
- Beaking of anterior part of T_{12} & L_1 vertebrae.

Cardiac

- ECG shows bradycardia and low voltage.
- Echo / Chest x ray may show cardiac enlargement and effusion.

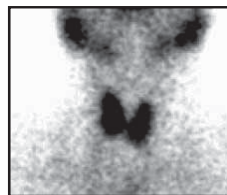
Others

- High serum cholesterol/ Macrocytic anemia

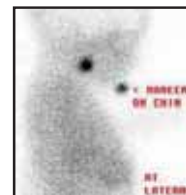
3. For the cause

a. Thyroid scintigraphy (using radioactive ^{123}I):

- Absent uptake in:
 - Aplasia
 - Iodide trapping defect
- Normal or increased uptake in dysmorphogenesis.
- Can localize ectopic thyroid.



Normal thyroid position



Lingual thyroid in an infant



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- b. TRH stimulation test: (performed only with ↓ TSH)
 - Differentiate between hypothalamic & pituitary defects
 - Give an i.v. bolus of TRH:
 - If T4 increases → hypothalamic defect i.e. Tertiary hypothyroidism
 - If T4 does not increase → pituitary defect i.e. Secondary hypothyroidism
- c. Skull CT & MRI for pituitary tumors.

Treatment

- Replacement therapy with sodium L-thyroxin (Eltroxin 50 µg tablet) for life
- Dose: **10-15 µg/kg/day** in neonate (start with the higher dose if T4 < 5 µg/dl)
6 - 8 µg/kg/d in infant
4 µg/kg/d in child
- Follow up and monitoring
 - Clinical: for activity, milestones, growth and overtreatment
 - Lab: for T₄ and TSH (done monthly in the first 6 mo of life, then 3 monthly)
 - Radiologic: monitor bone age

NB

- Overtreatment carries risk of craniosynstosis and temperament disorders
- To rule out *transient hypothyroidism*:
 - Discontinue treatment at 3 years for 3-4 weeks and test for TSH; it will shoot in permanent hypothyroidism
 - This test is unnecessary in:
 1. Infants with proven thyroid ectopia
 2. In those who manifest elevated levels of TSH after 6-12 mo of therapy because of poor compliance or an inadequate dose of T4

Prognosis

- Diagnosis & treatment before 3 months → normal linear growth and intelligence
- Delay in diagnosis, failure to correct initial hypothyroxinemia rapidly, inadequate treatment, and poor compliance in the first 2-3 yr of life result in variable degrees of brain damage.
- Without treatment, affected infants are profoundly mentally deficient and growth retarded
- As diagnosis of hypothyroidism is difficult in the first 3 months screening for thyroid function (usually TSH) in all neonates is done in the first week of the life

Acquired Hypothyroidism

Definition: Juvenile hypothyroidism with manifestations appearing after the 1st year.(After a period of normal thyroid function).

Causes

1. Thyroiditis

- Autoimmune thyroiditis(Hashimoto disease; chronic lymphocytic thyroiditis):
 - The most common cause of thyroid disease in children and adolescents. It is also the most common cause of acquired hypothyroidism, with or without goiter
 - May be part of polyglandular auto immune syndromes (associated with e.g. DM, Addison)
 - Children with Down, Turner, and Klinefelter syndromes and celiac disease or diabetes are at higher risk for associated autoimmune thyroid disease
- Suppurative.
- Viral e.g. mumps.

2. Injury to thyroid → trauma, surgery, irradiation, cystinosis

3. Iodine containing drugs e.g. cough mixtures.

Clinical picture

- Poor academic progress; but no mental retardation
- Unexplained short stature
- Skin: cold, pale(*refractory anemia*), excess myxoedematous tissue
- Cold intolerance
- Constipation
- Delayed puberty (may be precocious).

Investigations

As before but

- a. Search for auto antibodies for Hashimoto thyroiditis e.g.
 - Thyroid antiperoxidase antibodies (TPO-Abs) and Antithyroglobulin antibodies (anti-Tg Abs)
 - TSH blocking antibody (may identify patients at future risk of having babies with transient congenital hypothyroidism).
- b. Check for associated auto immune disorders e.g. auto immune hepatitis, diabetes mellitus, Celiac disease, Addison disease

Treatment:

- Overt hypothyroidism (elevated TSH, low T4 or free T4), require replacement treatment with levothyroxine
- For subclinical hypothyroidism (elevated TSH, normal T4 or free T4), many clinicians prefer to treat such children until growth and puberty are complete, and then reevaluate their thyroid function

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Causes of deafness & hypothyroidism**1- Pendred syndrome**

Mutation in the chloride-iodide transport protein common to the thyroid gland and the cochlea → impaired iodide organification, & positive perchlorate discharge test → Sensorineural deafness and Goitrous hypothyroidism



2- Endemic goiter

3- Neglected hypothyroidism

4- Congenital rubella syndrome

Short Stature

- Growth is strongly related to the genetic potential. A child's target height (TH) is calculated by Mid Parent Height as follows:
 - Girl = (height of mother in inches + height of father in inches)/2 - 2.5inches
 - Boy = (height of mother in inches + height of father in inches)/2 + 2.5inches
- Short stature is height below 3rd percentile for age and sex
- Short stature is either:

Proportionate	Disproportionate
<ul style="list-style-type: none"> - Upper segment/lower segment is normal for age - Height equals span 	<ul style="list-style-type: none"> - Upper segment/lower segment is abnormal for age. - Height does not equal span

I. Proportionate Short Stature

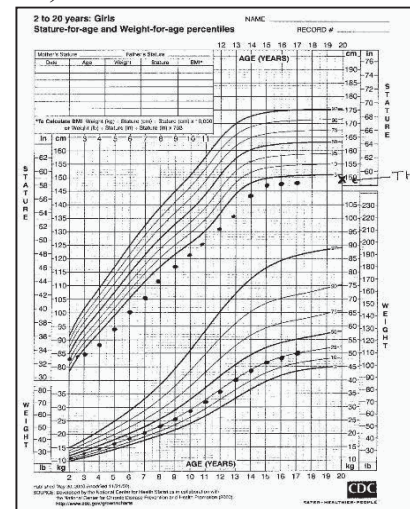
A. Normal types of short stature (about 90% of cases)

1. Familial (genetic) short stature

A short child who is growing close to his/her target height percentile

Clues:

- Small birth length (normal for the family)
- Normal bone age and age of onset of puberty
- Short parents (familial)
- Short target height like their parents

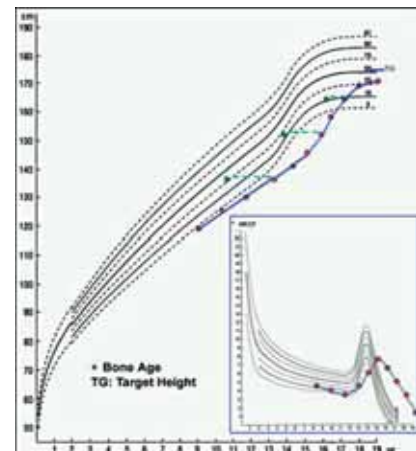


2. Constitutional Growth Delay (CGD)

Growth is normal for the 1st 4-12 mo of life. Height is sustained at a lower percentile during childhood with acceleration late in adolescence when their peers stop growing leading to a final height that is close to the target height

Clues:

- Delayed bone and age of onset of puberty
- Other family members (often one or both parents) with histories of short stature in childhood, delayed puberty, and eventual normal stature
- IGF-1 levels tend to be low for chronological age but normal for bone age



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B. Pathologic types:

- ❶ Chronic undernutrition → marasmus & nutritional dwarfism
- ❷ Chronic systemic disease
 - Malabsorption syndrome e. g celiac disease, inflammatory bowel disease
 - Chronic hemolytic anemia e.g. thalassemia
 - Chronic renal failure, renal tubular acidosis, urinary tract infections.
 - Chronic chest diseases e.g. cystic fibrosis, asthma
 - Chronic heart diseases: congenital, rheumatic, cardiomyopathy
- ❸ Endocrinal causes:
 - Hypothyroidism.
 - Hypopituitarism.
 - Hypercortisolism (Cushing syndrome) and adrenal insufficiency
 - Precocious puberty
 - Diabetes mellitus.
 - Diabetes insipidus.
- ❹ Psychosocial dwarfism:
 - Due to maternal neglect or emotional deprivation
 - Evidence of functional hypopituitarism is indicated by low levels of IGF-1 and suboptimal GH on provocation
 - History and careful observations reveal disturbed mother-child or family relations
 - Associations: perverted or voracious appetites, enuresis, encopresis, insomnia, crying spasms, and sudden tantrums
- ❺ Syndromes with short stature e.g.:

- Turner	- Noonan
- Down	- Other trisomies; e.g. 13 , 18
- Prader Willi	- Silver Russell
- ❻ Intra uterine growth retardation: 10 –15% will be short.

II. Disproportionate Short Stature

A. With short limbs e.g.

- Achondroplasia
- Rickets
- Osteogenesis imperfecta

B. With short trunk e.g.

- Skeletal dysplasia e.g. Ectodermal dysplasia and Morquio s syndrome
- Fanconi anemia

Approach to Diagnosis

I. History

* Perinatal for:

- Exposures; infections, maternal drugs
- Birth weight and length (differentiate prenatal and postnatal causes)
- Problems e. g. microphallus & hypoglycemia in hypopituitarism.

* Past history suggestive of:

- Chronic systemic disease.
- Endocrinal disorder

* Dietetic history for under nutrition or eating disorders.

* Family history for parent's height, other short siblings and social problems

II. Examination

Clinical tests

- Check parent's height → to rule out genetic causes.
- Determine type of short stature → proportionate or disproportionate
- Plot patient weight and height on growth charts:

1. Short stature following own growth curve:

- a. Familial short stature
- b. Constitutional growth delay

2. Short stature with decelerating growth pattern

Weight for age < height for age	Weight for age > height for age
<ul style="list-style-type: none"> - Chronic systemic disease - Chronic undernutrition - Cardiac disease 	<ul style="list-style-type: none"> - Endocrinopathy e.g. Hypothyroidism Cushing , Hypopituitarism - Syndromes - Skeletal dysplasia

3. Short stature with normal weight for height: Emotional deprivation

Clinical examination

- Evaluate nutritional state: check for muscle wasting, subcutaneous fat loss and signs of vitamin deficiencies.
- Complete systemic examination: including cardiac, chest, abdomen, neurologic
- Check for features suggesting endocrinal disorders e.g. hypothyroidism.
- Check for dysmorphic features e.g. Down, Turner

III. Investigations

- Assess bone age by left wrist X-ray:
 - Normal in familial short stature
 - Delayed in most other causes

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- Search for systemic diseases by:
 - Urine analysis → for glucosuria, UTI, osmolality
 - Stool analysis → for malabsorption
 - CBC → for anemia
 - ESR → increased in infection & inflammation.
 - Urea, creatinine → for renal failure
 - Chest X-ray → for suspected chest disease
 - Echocardiography → for suspected cardiac defect
 - Serum pH, calcium, phosphate for metabolic bone disease
 - Specific e.g. Celiac screen, malabsorption workup, chromosomal studies

3. Hormonal assay:

- Free T4 & TSH for hypothyroidism (Because thyroid hormone is necessary for normal GH synthesis, it must always be assessed before GH evaluation)
- Provocative growth hormone level & IGF-1 for hypopituitarism
- Night time blood or salivary cortisol level for Cushing
- Blood glucose for diabetes
- Serum & urine osmolality for diabetes insipidus

Treatment

1. Treat the cause e.g.
 - Gluten free diet for celiac
 - EL-troxin for hypothyroid
2. Recombinant growth hormone

“FDA approved indications of GH therapy”:

 - GH deficiency
 - Turner syndrome
 - Chronic renal failure before transplantation
 - Idiopathic short stature
 - Small-for-gestational age short stature
 - Prader-Willi syndrome
 - Noonan syndrome
3. Adequate balanced diet
4. Psychologic support

Diabetes Mellitus

Definition:

- Chronic, metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature
- Deficiency of insulin or its action with subsequent defect in metabolism of carbohydrates, protein & lipids

Actions of insulin

- ↓ Blood glucose by → ↑ Glucose uptake by cells
→ ↓ Gluconeogenesis
→ ↓ Glycogenolysis
- ↑ Lipogenesis
- Anabolic effect

Types of diabetes mellitus

1. Insulin dependent (Type 1 DM)
2. Non-insulin dependent (Type 2 DM)
3. Secondary diabetes mellitus:
 - Endocrinopathies: Cushing disease, Hyperthyroidism, Acromegaly
 - Drug- or chemical-induced: Steroids, Thyroid hormone
 - Diseases of the exocrine pancreas: Hemochromatosis, Cystic fibrosis, Pancreatitis

Criteria for diagnosis

	Fasting plasma glucose	2-hr plasma glucose during the OGTT
• Diabetes mellitus	≥ 126 mg/dL (7.0 mmol/L)	≥ 200 mg/dL
• Impaired glucose tolerance	100-125 mg/dL	≥ 140 mg/dL, but < 200 mg/dL

OGTT: Oral Glucose Tolerance Test, Values in mg/dl

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Insulin dependent diabetes mellitus

Etiology

β -cell destruction leading to absolute insulin deficiency, may be related to:

- Genetic predisposition: associated with HLA -DR₃, DR₄
- Auto immune response (Humoral & cell mediated response against islet cells):

Evidence:

- Presence of Islet cell autoantibodies
- Association with other auto immune diseases e.g. thyroiditis
- Environmental factors:
- Viral infection e.g.: mumps, rubella, measles, EBV

Pathogenesis

Insulin deficiency results in disturbance of carbohydrate, fat & protein metabolism.

- Fat metabolism: \downarrow Lipogenesis \rightarrow \uparrow free fatty acids (FFA) \rightarrow \uparrow Ketone bodies
- Carbohydrate metabolism:
 - Hyperglycemia due to
 - \downarrow glucose uptake & utilization by the cells
 - \uparrow gluconeogenesis & glycogenolysis
 - Hyperglycemia leads to osmotic diuresis \rightarrow polyuria & polydipsia
- Protein metabolism: \uparrow proteolysis \rightarrow \downarrow body weight.

Clinical picture

- Polyuria, polydipsia, polyphagia & weight loss.
- Diabetic keto-acidosis (DKA) is the presenting feature in 25% of cases (10% in T2DM).
- Secondary nocturnal enuresis

Diagnosis of diabetes mellitus

- Symptoms of diabetes mellitus (include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria) **plus** random plasma glucose \geq 200 mg/dL (11.1 mmol/L)

or

- Fasting (at least 8 hr) plasma glucose \geq 126 mg/dL (7.0 mmol/L)

or

- 2-hr plasma glucose during the OGTT \geq 200 mg/dL

or

- Hemoglobin A1C \geq 6.5% (*Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia*)

(Nelson textbook of pediatrics 2016)

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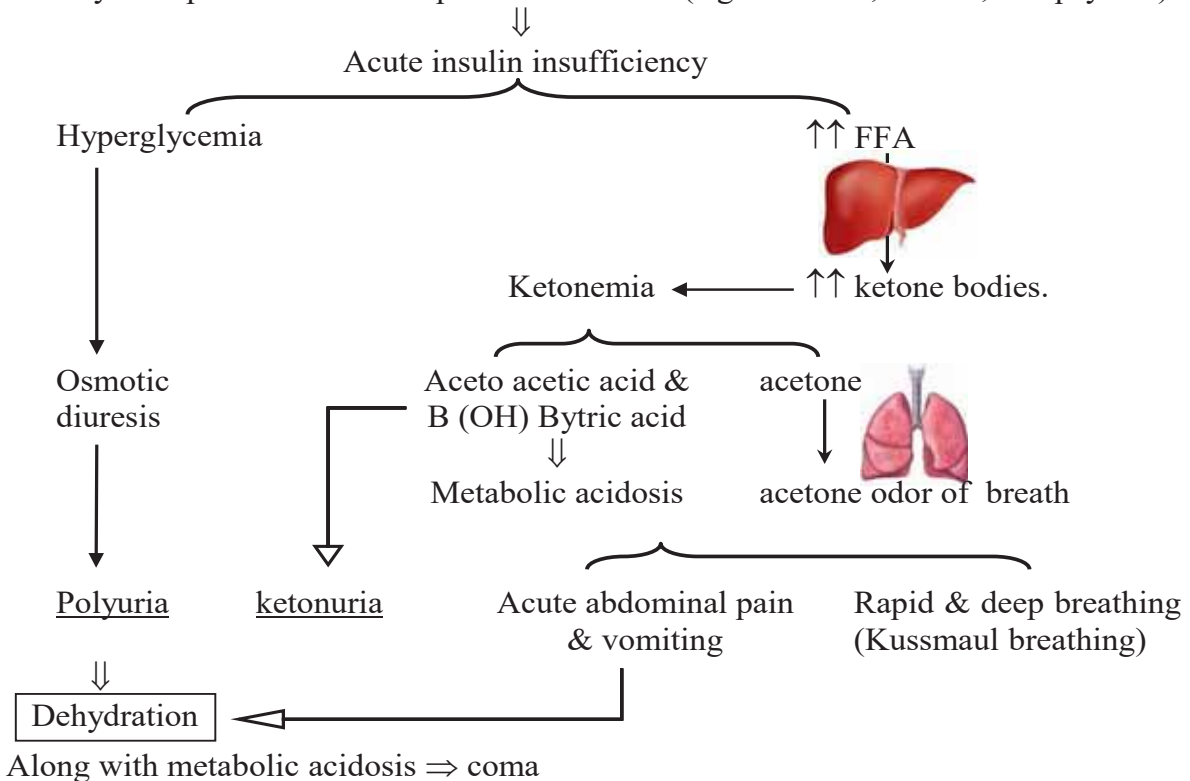
Diabetic Keto Acidosis (DKA)

Definition

- Metabolic disorders due to *acute* insulin insufficiency
- Risk Factors:
 - Omission of insulin dose by error or during inter current illness
 - Insulin pump failure
 - Adolescent girls
 - Psychiatric disorders including eating disorders
 - Previous DKA

Pathogenesis

History of exposure of diabetic patient to stresses (e.g. infection, trauma, and psychic).



Clinical stages of DKA

Early	Then	Later
<ul style="list-style-type: none"> – Polyuria – Nausea and vomiting – Abdominal pain mimicking an acute abdomen 	<ul style="list-style-type: none"> – Dehydration – Rapid, deep, sighing (Kussmaul) breathing 	<ul style="list-style-type: none"> – Progressive obtundation – Impaired consciousness

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Diagnosis

Diagnostic criteria of DKA

- Diabetic → Hyperglycemia ; blood glucose >200 mg/dL [\approx 11 mmol/L]
- Keto → Ketonemia and ketonuria
- Acidosis → Venous pH <7.3 and/or bicarbonate <15 mmol/L

Severity of DKA

Mild	Venous pH 7.25-7.35 Or Bicarbonate 16-20 mmol/L Clinical: Oriented, alert but fatigued
Moderate	Venous pH 7.15-7.25 Or Bicarbonate 10-15 mmol/L Clinical: Kussmaul respirations; oriented but sleepy; arousable
Severe	Venous pH <7.15 Or Bicarbonate <10 mmol/L Clinical: Kussmaul or depressed respirations; depressed sensorium to coma



Management

- Assess
 - Severity of dehydration (most cases are considered 5- 8% dehydrated)
 - Level of consciousness using Glasgow coma scale
- Request
 - Plasma glucose, HbA1c, urinalysis for ketones, blood β -hydroxybutyrate and venous pH
 - Electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, and magnesium concentrations
 - CBC and cultures (blood, urine) if infection is suggested
 - ECG for baseline evaluation of potassium status

A. Acidotic phase (in ICU)

DKA is a medical emergency that should follow ABC scheme

Admit to the ICU

Airway 	<ul style="list-style-type: none"> – Secure the airway – Insert airway in comatose – Insert nasogastric tube if conscious level depressed or the child is vomiting
	<ul style="list-style-type: none"> – 100% O₂ for hypoxia – \pm intubation and ventilation
Breathing 	<ul style="list-style-type: none"> – Site 3 IV lines one for I.V fluids , a 2nd for I.V insulin and a 3rd sampling cannula – Obtain blood sample for investigations – Give antibiotics to febrile patients

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Monitoring using flow sheet

Hourly <ul style="list-style-type: none"> – Vital signs – Neurologic state for warning signs of cerebral edema and Glasgow coma scale if comatose – Cardiac monitor for potassium status – Capillary blood glucose – Amount of insulin – Fluid input and output (catheter) 	Two hourly lab tests for the first 12 hours <ul style="list-style-type: none"> – Glucose – Blood gases – Blood β-hydroxybutyrate – Serum electrolytes – Blood urea nitrogen – Calcium, magnesium, phosphorus
Urine ketones until cleared	Weigh the patient twice a day

1. Fluid therapyShock therapy

- 10 ml/kg over 1 hour can be repeated up to 30 ml /kg
- 0.9% saline or lactated ringer



In the 2nd hour after the shock therapy and until resolution of DKA:

- Fluid requirement = Fluid maintenance + Fluid deficit (85 ml/kg) – Boluses fluids given over next 23 hour (36 hours in severe cases)

N.B

- Fluid deficit = % Dehydration \times Body weight
- Fluid maintenance (24hr) = 100ml/kg (for the 1st 10 kg) + 50ml/kg (for the 2nd 10) + 25 ml/kg (for all remaining kg)
- Replace any ongoing fluid loss in vomiting or diarrhea or massive polyuria

Type of fluid

- 0.45% NaCl plus 20 mEq/L K phosphate and 20 mEq/L K acetate
- If K < 3 mEq/L, give 0.5 to 1.0 mEq/kg as oral K solution OR increase IV K to 80 mEq/L
- Bicarbonate therapy is rarely necessary and may even increase the risk of hypokalemia and cerebral edema

2. Insulin therapy

- Use regular insulin (e.g. Actrapid)
- Slow infusion **0.1** unit/kg/hour without bolus must be given *at the beginning of therapy*
- Prepared by adding 50 units (0.5 ml) soluble insulin to 49.5 ml 0.9% saline in 50 ml syringe pump to provide 1 unit/ml concentration and insulin started at **0.1ml/kg/hour**

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▪ Precautions with insulin therapy

If the blood glucose concentration drops too quickly before the DKA has resolved:

- Serum glucose has decreased $< 300 \text{ mg/dL}$ → Glucose is added as a 5% solution
- Serum glucose has decreased $< 200 \text{ mg/dL}$ → Glucose is added as a 10% solution
- If the serum glucose falls further despite these interventions, → The insulin infusion can also be lowered to 0.05 U/kg/hr



Aim to keep blood glucose at about 11 mmol/L (200 mg/dL) until resolution of DKA

▪ Shift to oral intake and subcutaneous insulin

- ✓ When DKA has resolved indicated by:
 - Bicarbonate $> 15 \text{ mEq/L}$; pH > 7.30
 - Sodium stable between 135 and 145 mEq/L
 - No emesis
- ✓ Subcutaneous insulin
 - Dose: $0.2\text{--}0.4 \text{ u/kg}$ every 6-8 hr
 - To prevent rebound hyperglycemia the first injection should be given 30 minutes before stopping the insulin infusion

3. Treat precipitating factors e.g. Antibiotics for infections.

Hazards during treatment of DKA

1. **Cerebral edema**

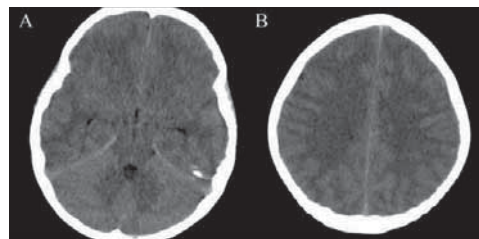
Warning clue

Serum sodium should increase by about 1.6 mmol/L for each 100 mg/dL decline in the glucose; the sodium should steadily increase with therapy.

Declining sodium may indicate excessive free water accumulation and the risk of cerebral edema

Signs of cerebral edema

- Headache & slowing of heart rate
- Change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
- Specific neurological signs (e.g., cranial nerve palsies)
- Rising blood pressure
- Decreased O₂ saturation



Treatment

- Initiate treatment as soon as the condition is suspected.
- Reduce the rate of fluid administration by one-third.
- Give mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes to 2 hours
- Hypertonic saline (3%), 5–10 mL/kg over 30 minutes, may be an alternative to mannitol or a second line of therapy if there is no initial response to mannitol
- Elevate the head of the bed
- Intubation may be necessary for the patient with impending respiratory failure

1. Hypokalemia.

2. Severe hypophosphatemia

3. Hypoglycemia

Hint: "I myself prefer adopting the British Society of Paediatric Endocrinology and Diabetes protocol for DKA, 2015. It is very easy and less complicated.

Please google it"

Mohamed El Koumi

Mortality rate of DKA: About 0.2% due to:

- Cerebral edema accounts for 60% to 90% of all DKA deaths
- Hypokalemia induced arrhythmias
- Sepsis / aspiration pneumonia

Differential diagnosis: From other causes of coma in diabetic child:

A. Hyperosmolar non ketotic coma (Hyperglycemic hyperosmolar state;HHS)

- Plasma glucose concentration >33.3 mmol/L (600 mg/dL)
- Arterial pH >7.30
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to mild ketonemia
- Effective serum osmolality >320 mOsm/kg
- Clinically : Stupor or coma, severe dehydration

B. Hypoglycemic coma

- History :
 - Known diabetic with insulin overdose or exercise or delayed meals
- Clinically
 - Reactive sympathetic stimulation (↑catecholamines): Pallor, hunger pains, tachycardia, sweating, jitteriness, tremor, irritability
 - Glucopenia of CNS: Lethargy, limpness, may be seizures.
- Blood glucose < 50 mg/dl (< 2.6 mmol /l)
- Rapid response to I.V. glucose

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B. Post acidotic phase

Regular Insulin	Diet
<ul style="list-style-type: none"> – Dose: 0.2-0.4 u/kg/ 6-8 hrs; SC – Given 0.5 -1 hr before meals – Increase or decrease insulin dose by 10% to keep blood glucose between 100-180 mg/dl 	<ul style="list-style-type: none"> – Seek dietitian advice – Sips of water – Skimmed milk – Dietetic juice – Two days later give average diet

C. Lifelong management**1. Insulin**

Starting Doses of Insulin (units/kg/day)

	No DKA	Post DKA
▪ Prepubertal	0.25-0.50	0.75-1.0
▪ Pubertal	0.50-0.75	1.0-1.2
▪ Postpubertal	0.25-0.50	0.75-1.0

Types

- Short acting
 - Regular insulin (Crystalline insulin, Humulin R)
 - Ultra short acting: Insulin Aspart (Novorapid) / Lispro (Humalog)
- Intermediate insulin (NPH, insulin Monotard , Humulin N)
- Long acting insulin (Glargine ; Lantus and Detemir)

Regimens**1. Multiple dose injections** (recent, very effective):

- Use Glargine or Detemir as basal insulin at bed time
- The basal insulin should be 25-30% of the total dose in toddlers and 40-50% in older children
- The remaining insulin is given as pre meals boluses of ultra-short acting analogs (usually Novorapid or Humalog) based on carbohydrate in meals

2. Two injections regimen:

- 2/3 the total daily dose before breakfast
- 1/3 the dose before evening meal
- Each dose contain 1/3 short acting analog & 2/3 NPH

3. Three injection regimen:

- NPH and short acting analog bolus at breakfast
- Short acting analog bolus alone before afternoon snack or the main evening meal
- NPH at bed time

4. Continuous subcutaneous insulin infusion using automated insulin pump

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Adjustment:

Increase or decrease insulin dose by 10% to keep blood glucose:

- Pre meal 70-145 mg/dl
- Post prandial (1-2 hours) < 180 mg/dl
- Pre bed time 125-180 mg/dl

2. Instructions

- Diet → 3 main meals with 2 snacks (engage a dietician expert in diabetics diets).
- In infections increase rapid acting insulin by 10%
- Decrease insulin before exercise

3. Monitora. Daily blood glucose at least 4 times

- Before breakfast, lunch, supper & at bed time.
- Initially test blood glucose also between 12AM & 3AM to exclude nocturnal hypoglycemia

b. Glycosylated hemoglobin (Hb A_{1C}).

- Fraction of hemoglobin to which glucose has been attached.
- Measured as a percent of total hemoglobin.
- Value: Reflect average blood glucose over previous 2-3 months:
 - Normal, non-diabetic → < 6%
 - American diabetes association recommends:
 - Hb A_{1C} of < 8.5 % in toddlers
 - Hb A_{1C} of < 8 % in children
 - Hb A_{1C} of < 7.5 % in teenagers

Honey moon period

* Due to residual β -cell function → release insulin **so** About 75% of new diabetics complain recurrent hypoglycemia which may recur for weeks to months.

* Advice: Never stop insulin but reduce the dose to avoid hypoglycemia.

Somogi phenomenon

* Due to large insulin dose > 2 u/kg/d → Late nocturnal hypoglycemia occur → ↑↑ anti insulin hormones → early morning hyperglycemia.

* Advice: Reduce the evening intermediate insulin by 10%

Dawn phenomenon

* Due to overnight growth hormone secretion → antagonise insulin action → early morning hyperglycemia.

* Advice: Increase the evening intermediate insulin by 10%

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Polyuria

Definition: Passage of excessive urine output > 2 liters/m²

Causes

Endocrinal	Renal	Psychogenic
* Diabetes mellitus * Diabetes insipidus	* Hypokalaemia (< 2.5 meq/l). * Renal tubular acidosis * Bartter syndrome * Hypercalcemia (> 13 mg/dl). * Chronic renal failure.	* Compulsory water ingestion

Diabetes Insipidus

Definition

Inability to produce concentrated urine due to either

1. Decrease ADH production \Rightarrow Neurogenic diabetes insipidus.
2. Lack of response of renal tubules to ADH \Rightarrow nephrogenic diabetes insipidus.

Clinical picture

i- Polyuria = Urine output : 4-10 Liter/day.

- Polydipsia (Irritable infants)
- 2ry nocturnal enuresis.
- If water inaccessible \rightarrow Dehydration
 - \rightarrow Electrolyte disturbance.
 - \rightarrow Fever (no sweating).
 - \rightarrow Shock in severe cases.

ii- Growth retardation

iii- May be features of the cause e.g \uparrow ICT in craniopharyngioma

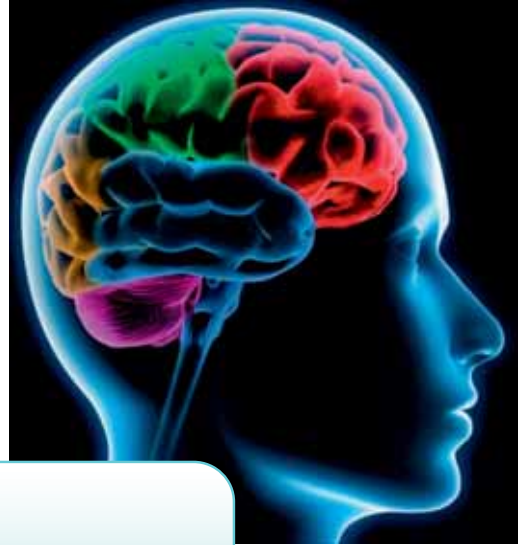
Investigations

1. Urine:
 - Specific gravity: 1002-1005 (diluted)
 - Osmolality: low (50-200 m.osmol/L)
 - No pathological constituents
2. Plasma osmolality: High (> 295 m.osmol /L)
3. Water deprivation test.
4. Vasopressin stimulation test

Treatment

- ◆ Neurogenic \rightarrow Desmopressin intranasal twice daily
- ◆ Nephrogenic \rightarrow Adequate hydration.
 - \rightarrow Correct hypokalemia by:
 - Oral potassium.
 - Potassium sparing diuretics.
 - \rightarrow Indomethacin .

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Neurology

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الدفعة ال14

Meningitis

Definition: Inflammation of the membranes covering the brain & spinal cord.

Types:

- Bacterial
- Aseptic e.g. viral, fungal
- Tuberculous

Bacterial (Septic) meningitis

Causes

	G -ve bacteria	G +ve bacteria	
Cocci	<ul style="list-style-type: none"> • Nisseria meningitidis type A, B, C, D, Y, W 135** 	<ul style="list-style-type: none"> • Pneumococci • Staphylococci • Streptococci 	} ++ in infants & children
Bacilli	<ul style="list-style-type: none"> • E.coli • Hemophilus influenza. 	<ul style="list-style-type: none"> • Listeria monocytogenes 	} ++ in neonates

N.B. ** Serogroup B is responsible for more than 50% of cases in children less than 1 year and has also been associated with outbreaks on college campuses

Transmission: - Droplet infection mostly (Blood borne in neonatal sepsis)

Clinical picture

1. Non specific

- High fever (may be hypothermia in neonates).
- Poor feeding
- Rose spots may appear on the trunk & extremities in meningococcal septicemia.

2. Features of increased intracranial pressure (ICP)

- Before fontanel closure → tense, bulging anterior fontanel
- After closure of fontanel:
 - Severe bursting headache (irritability)
 - Blur of vision
 - Projectile vomiting (in the morning, not preceded by nausea)
 - Cushing response (hypertension & bradycardia)

3. Features of meningeal irritation: (less sensitive in infants)

- Neck rigidity (stiffness) → limited neck flexion
- Opisthotonus → arched back
- Kernig's sign → inability to extend the leg after the thigh is flexed to a right angle with the axis of the trunk.
- Brudzinski leg sign: Passive flexion of one hip → flexion of the other hip and knee
- Brudzinski neck sign: Passive flexion of the neck → flexion of the hip & knee.

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4. Neurologic signs

- Stupor & drowsiness
- Convulsions → usually generalized
- Coma

Clinical types

- 1- Meningitic form → the classic presentation as before.
- 2- Fulminant meningitis.
 - Abrupt fever.
 - Severe headache and convulsions.
 - Rapidly progress to coma.
 - Fatal within 48 hrs.
- 3- Septicemic form (usually complicating meningeococcal form)
 - Very bad general condition
 - Shock
 - Purpura & ecchymosis
 - Meningitis develop within 1-2 days (**or** not at all)

Complications

- 1- Syndrome of inappropriate secretion of antidiuritic hormone (SIADH) → so, maintenance fluids must be at 2/3 normal to avoid brain edema.
- 2- Neurologic complications:
 - Increased intracranial pressure (ICP) → May leads to cerebral or cerebellar herniation
 - Subdural effusion
 - Cranial nerve lesions (commonly oculomotor, 6th & 8th nerves).
 - Hydrocephalus.
- 3- Peripheral circulatory complications
 - i- Waterhouse Friedrichson syndrome
 - Septicemia
 - Shock
 - Extensive purpura
 - Adrenal hemorrhage (acute adrenal failure).



- ii- DIC: Gangrenous patches & extremities

- 4- Dissemination of infection: endocarditis, arthritis, osteomyelitis

Investigations

1. CBC → Leukocytosis (↑↑ PMNL)
2. Blood culture reveals the responsible bacteria in up to 80-90% of cases

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3. C-reactive protein, ESR, and procalcitonin have been used to differentiate bacterial (usually elevated) from viral causes of meningitis

4. Lumbar puncture (LP) & CSF examinations:

Value

- Diagnostic (Discover organism, ↑PMNL, ↑Protein, ↓Glucose)
- Determine appropriate antibiotics by culture & sensitivity.
- Evaluate treatment: CSF become sterile within 24- 48 hours of appropriate antibiotics

Contraindications for an immediate LP

1. Evidence of increased ICP (other than a bulging fontanel), such as 3rd or 6th cranial nerve palsy with a depressed level of consciousness, or hypertension and bradycardia with respiratory abnormalities
2. Severe cardiopulmonary compromise requiring prompt resuscitative measures for shock
3. Infection of the skin overlying the site of the LP

What to do if an LP is delayed?

- Initiate empirical antibiotic therapy
- CT scanning for evidence of a brain abscess or increased ICP
- LP may be performed after increased ICP has been treated

Condition	Appearance	Pressure (mmH ₂ O)	Protein (mg/dl)	Glucose (mg/dl)	Leukocytes / ml	Organism
Normal CSF	Clear	50 - 80	5 – 20	40-80	0-5 (monocytes)	Nil
Bacterial meningitis	Turbid	↑↑	↑↑ (> 100)	↓↓	↑↑ (100-60.000) Mainly PMNLs	+ve Gram stain* +ve culture
TB meningitis	Web On stand	↑↑	↑↑ (> 100)	↓↓	↑ (10-500) Early PMNLs then lymphocytes	Acid fast bacilli by zehl nelsen stain.
Viral meningitis	Clear	Normal or slightly ↑	Mild ↑ (< 100)	Normal or ↓↓	↑ (10-500) Early PMNLs later mononuclear cells predominate	Viruses may be isolated

* Gram stain is positive in 70-90% of patients with untreated bacterial meningitis

N.B: In *partially treated meningitis*

- ✓ Culture and gram stain are usually negative
- ✓ But Pleocytosis with a predominance of neutrophils, elevated protein level, and a reduced CSF glucose usually persist for several days

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Differential diagnosis

- 1- From other causes of meningitis
- 2- Meningism:
 - Noninfectious meningeal irritation due to extra cranial lesions
 - Causes: Upper lobe pneumonia, otitis media, shigellosis
 - CSF is normal
- 3- Brain abscess
- 4- Encephalitis

Management**A. Treatment****1. Antibiotic therapy**

- Parenteral antibiotics according to culture and sensitivity for 2- 4 weeks
- Empirical therapy while waiting for culture results:
 - ✓ Third-generation cephalosporins (cefotaxime 300mg/kg/day divided 6 hourly **or** ceftriaxone 100mg/kg/day)
 - Plus**
 - ✓ Vancomycin (60 mg/kg/24 hr, given every 6 hr)
 - ✓ If a patient is immunocompromised and Gram-negative bacterial meningitis is suspected, initial therapy might include ceftazidime and an aminoglycoside or meropenem
 - ✓ If *Listeria monocytogenes* infection is suspected, as in young infants ,give ampicillin (200 mg/kg/24 hr, given every 6 hr)

2. Supportive therapy

(Nelson 2016)

Measures to ↓ ICP

- Mannitol 0.5 –1gm/kg iv
- Furosemide 1mg/kg iv

Corticosteroids**Indications:**

- a. H. influenza meningitis:
 - Value: Reduce inflammatory response caused by cell lysis
 - Use dexamethasone 0.15 mg/kg/dose every 6 hours for 2 days
 - Maximum benefit if given 1-2 hr before antibiotics are initiated
- b. Septic shock to improve general condition.
- c. Adrenal failure

Treatment of complications e.g. convulsions

- Immediate relief by diazepam or lorazepam
- Then phenytoin loading and maintenance

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B. Prevention

- Isolation of the case
- Vaccination against H.influenza, meningococci, pneumococci
- Chemoprophylaxis for contacts: e.g. rifampicin 10-20 mg/kg/day \Rightarrow for 2-4 days.

Prognosis Depends on:

- 1- Age: the younger the age, the worse the prognosis.
- 2- Course: fulminant meningitis has worse prognosis.
- 3- Cause:
 - E.coli & staph \rightarrow \uparrow fatality & \uparrow long term sequelae.
 - H.influenza & pneumococci \rightarrow moderate prognosis.
 - Meningococci \rightarrow $< 5\%$ fatality & no residual disability.

Aseptic meningitis

Meningitis with no micro organisms detected in CSF by gram stain or bacterial culture.

- Causes:**
- Mostly viral
 - Herpes simplex virus
 - Enteroviruses (Echo & coxsackie)
 - Mumps
 - Epstein barr virus
 - Protozoa
 - Malaria
 - Toxoplasma
 - Non infectious
 - CNS leukemia
 - Intrathecal injection
 - Post vaccination.

Diagnosis: - CSF analysis
- Viral isolation

Treatment: - Supportive ± antiviral.

Seizures

Definition:

- A seizure is
 - Transient , paroxysmal, time limited, involuntary disturbance of brain function
 - Manifested by abnormal motor, sensory, behavioral or autonomic activities
 - With or without impaired consciousness

Causes

A. Acute Seizure

1. Febrile Seizure
2. First epileptic fit.
3. Symptomatic seizures
 - CNS causes:
 - Infection → meningitis, encephalitis, brain abscess.
 - Irritation → brain edema
 - Tumors of the brain
 - Toxic → tetanus, drug (e.g aminophylline), lead encephalopathy
 - Hemorrhage → trauma, hemorrhagic blood diseases.
 - Hypoxia → hypoxic ischaemic encephalopathy.
 - Hypertensive encephalopathy.
 - Metabolic causes:
 - Bilirubin encephalopathy
 - Uremic encephalopathy
 - Hepatic encephalopathy
 - Hypo (glycemia, calcemia, magnesemia)
 - Hypo **or** hypernatremia.
 - Pyridoxine (B₆) deficiency
 - Inborn errors of metabolism

B. Recurrent Seizures

1. Epilepsy
2. Symptomatic seizures
 - Tetany
 - Degenerative brain diseases
 - Chronic metabolic causes
 - Inborn errors of metabolism
 - Hepatic /Uremic encephalopathy

Febrile Seizures

Definition: Seizures in age vulnerable children due to:

- Rapid rise of body temperature.
- Due to extra cranial causes (mostly viral)

Incidence: - Affect 4% of children.

- Family history in about 20 % of cases (genetic base do exist)
- Recurrent in 30-50% of cases specially in those with family history

Diagnostic criteria

1. Age: 6 - 60 months (convulsions below or above this age is not febrile)
2. Fits occur within 8-12hrs from onset of fever.
3. No evidence of CNS infection (e.g. meningitis), nor metabolic disease
4. Evidence of extra cranial infection (e.g. tonsillitis, otitis media, roseola)
5. Occur in the absence of a history of prior afebrile seizures
6. Type of convulsions:

Simple (Typical)	Complex
<ul style="list-style-type: none"> - Generalized tonic-clonic. - Last < 15 min. - One fit only in the same illness. - The commonest form 	<ul style="list-style-type: none"> - Focal - Last > 15 min - Recurring within 24 hr - Uncommon.

Investigations

1. Lumbar puncture to rule out meningitis

Mandatory in

- Infants below 6 months presenting with fever and seizures
- Ill looking children
- Clinical suspicion of meningitis

Optional in

- Children 6-12 months not vaccinated for *Haemophilus influenzae type b* & *Streptococcus pneumonia* **or** immunization status is unknown
- Children who have been pretreated with antibiotics

2. EEG and Neuro imaging (CT, MRI)

- Only for cases with high risk of epilepsy ; usually not required for 1st simple febrile seizure
- EEG is done > 2 weeks of the attack

Risk of subsequent epilepsy is higher with:

- Neurodevelopmental abnormalities
- Complex febrile seizures (focal)
- Family history of epilepsy

3. Blood tests e.g. electrolytes, blood glucose if clinically indicated

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N.B: Major risk factors predicting recurrence of febrile seizures:

- Age <1 yr
- Duration of fever < 24 hr
- Fever 38-39 °C

Differential diagnosis

1. Intracranial infections: Meningitis, meningo encephalitis, and brain abscess
2. Epileptic fit precipitated by associated fever
3. Epilepsy syndromes typically start with febrile seizures e.g.
 - Generalized epilepsy with febrile seizures plus (**GEFS+**) : multiple febrile seizures and several types of afebrile generalized seizures
 - Severe myoclonic epilepsy of infancy (**Dravet syndrome**): seizures starts febrile then become afebrile with evolving developmental delay

Treatment

In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with one or more simple febrile seizures

1. Acute care of febrile seizure attack:

- Full history and thorough examination
- Fever control by paracetamol and tepid sponges or cold bath.
- Fit lasting more than **5** minutes → Diazepam, lorazepam, or midazolam
- Investigate and treat the underlying cause
- Treatment of *febrile status epilepticus*

2. Parent education about:

- Acute handling of seizures at home
- Seizures lasting > 5 minutes → rectal diazepam **or** buccal or intranasal midazolam
- Fever control → reduce the discomfort not the seizure recurrence
- During fever → intermittent oral diazepam 0.3 mg/kg q8 hours **or** rectal diazepam (0.5 mg/kg as a rectal suppository every 8 hr), reduce, but do not eliminate, the risks of recurrence of febrile seizures

(Nelson 2016)

Epilepsy

Epilepsy is

- A brain disorder with predisposition to generate seizures with neurobiologic, cognitive, psychologic, and social consequences of this condition
- It is considered to be present when
 - 2 or more unprovoked seizures occur in a time frame of longer than 24 hr
 - Or
 - At least 1 unprovoked epileptic seizure with enough EEG and clinical information to demonstrate recurrences

(Nelson 2016)

Causes

1. Idiopathic (Now termed genetic) in 80% of cases
2. Organic (secondary) in less than 20% of cases
 - Congenital cerebral malformation.
 - Degenerative brain diseases.
 - Post-traumatic, post-hemorrhagic, post-infection, post-toxic, post-anoxic

Classification

A. Focal (partial) seizures

* Only one part of the body is involved i.e. focal.

* Types:

1. Focal seizures without impairment of consciousness (Simple partial seizures)	2. Focal seizures with impairment of consciousness (Complex partial seizures)
<ul style="list-style-type: none"> ▪ No aura 	<ul style="list-style-type: none"> ▪ Often preceded by aura (e.g. visual hallucinations)
<ul style="list-style-type: none"> ▪ Brief 	<ul style="list-style-type: none"> ▪ Last 1-2 min
<ul style="list-style-type: none"> ▪ Motor (focal tonic, clonic or atonic) or sensory ▪ Often there is a motor (Jacksonian) march from face to arm to leg 	<ul style="list-style-type: none"> ▪ Only motor fits
<ul style="list-style-type: none"> ▪ No automatism ▪ DD: Tics: Unlike tics, motor seizures are not under partial voluntary control 	<ul style="list-style-type: none"> ▪ Automatism may occur → automatic semi purposeful movements of the mouth (oral, chewing) or of the extremities (manipulating the sheets, shuffling, walking).
<ul style="list-style-type: none"> ✓ Consciousness is intact. 	<ul style="list-style-type: none"> ✓ Consciousness is impaired with staring.
<ul style="list-style-type: none"> ▪ Postictal (Todd's) paralysis or sleepiness last minutes or hours 	

3. Focal seizures with secondary generalization

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4. Focal seizures epileptic syndromes:

- ***Benign childhood epilepsy with centrotemporal spikes (BECTS)***
 - Starts during childhood (ages 3-10 yr) and is outgrown in adolescence
 - The child typically wakes up at night owing to a focal (simple partial) seizure causing buccal and throat tingling and tonic or clonic contractions of one side of the face, with drooling and inability to speak but with preserved consciousness and comprehension
 - EEG shows typical broad-based *centrotemporal spikes* that are markedly increased in frequency during drowsiness and sleep
 - Drug of choice: Carbamazepine, oxcarbazepine
- ***Landau-Kleffner epileptic aphasia syndrome***
 - Focal seizures + verbal auditory agnosia and loss of speech
 - Drug of choice: Valproate

EEG in focal seizures

- ✓ Shows focal spikes or sharp waves in the lobe where the seizure originates.
- ✓ A sleep-deprived and 24-hour video EEG EEG increase diagnostic yield

B. Generalized seizures: The whole body is affected.

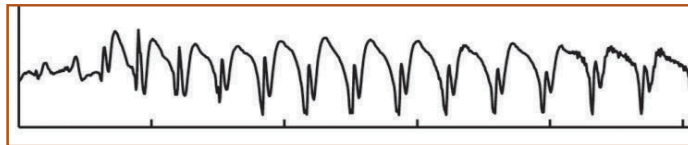
1. Absence seizures(Petit mal)

A. Typical Absence seizures

Incidence: More in girls. Usually start at 5-8 yr of age.

Description:

- Sudden cessation of all motor activities or speech with a blank facial expression; awareness of surroundings is cut off
- Accompanied by eye lid flutter or upward rolling of the eyes
- Last seconds; after seizure patient resume the pre seizure activity.
- Frequently recurrent; may occur countless daily
- No aura , loss of consciousness nor postictal phase
- EEG → typical 3 Hz spike-and-slow-wave discharges
- Hyperventilation for 3-5 min can precipitate the seizures and the typical EEG discharges



B. Atypical absence seizures

- Absences associated with myoclonic components **and** tone changes of the head (head drop) and body
- Precipitated by drowsiness
- Usually accompanied by 1-2 Hz spike-and-slow-wave discharges

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2. Generalized motor seizures (Grand mal)

The commonest form; pass in 3 phases.

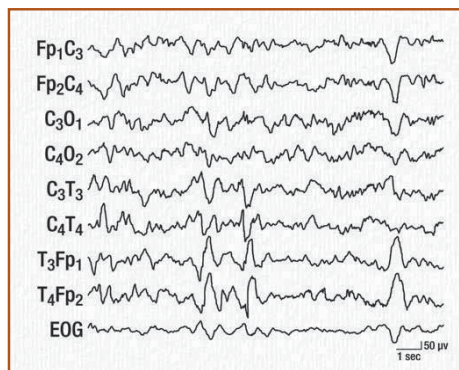
Aura (pre ictal phase)	Attack (ictal phase)	Post ictal phase
A warning signs before the attack may exist suggesting a focal origin of the epileptiform discharge: e.g. localized muscle spasm or paraesthesia.	<ul style="list-style-type: none"> – Sudden loss of consciousness – <u>Tonic phase</u>: tonic contraction of whole body → rigid posture, apnea, cyanosis, rolling of eyes & drooling of saliva. – <u>Clonic phase</u>: rhythmic contraction. & relaxation of all muscles groups → tongue biting & loss of sphincter control. 	<ul style="list-style-type: none"> – Semiconscious for 30 min-2hr. – Headache – Sleepiness

3. Myoclonic epilepsies

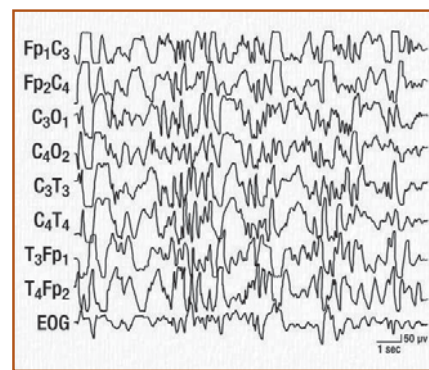
- Rapid shock like contractions, usually <50 msec in duration, that may be isolated or may repeat but usually are not rhythmic
- Intact consciousness.

4. Infantile spasms

- Starts in the 1st year of life
- Brief symmetric tonic contractions of the neck, extremities & trunk which may be flexor, extensor or mixed
- Repetitive; usually in the morning
- A cry may precede or follow the spasm; so may be confused with colic
- **West syndrome**: triad of infantile spasms, developmental regression, and a typical EEG ;hypsarrythmia (high-voltage, slow, chaotic background with multifocal spikes)
- **EEG** → Hypsarrythmias



Normal EEG



Hypsarrythmias EEG

5. Atonic or Astatic seizures

- Often follow myoclonic seizures
- Cause a very momentary loss of tone with a sudden fall

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Investigation

For the first unprovoked no febrile seizure

1. EEG (Electro Encephalogram); in awake and sleep state
2. Metabolic screen: Serum Na, Ca, Mg, glucose \pm inborn errors of metabolism
3. CSF examination in suspected CNS infections.
4. MRI (preferable) / CT brain for:
 - Patients with focal seizures
 - Increased intra cranial pressure
 - Resistance to treatment
5. ECG to rule out long QT or other cardiac dysrhythmias
6. Genetic diagnosis is now available for a huge number of seizures disorder

Treatment of epilepsy

▪ **When to start anti-epileptic drugs (AEDs)?**

<u>Low risk of recurrence</u>	<u>High risk of recurrence</u>
Isolated first seizure with: <ul style="list-style-type: none"> – Normal neurodevelopmental status – Normal EEG – Normal MRI – Absent family history of epilepsy 	Seizure with: <ul style="list-style-type: none"> – Abnormal neurodevelopmental status – Abnormal EEG – Abnormal MRI – Positive family history of epilepsy
✓ No long term AEDs ✓ Close observation ✓ Prescribe rescue medications (rectal diazepam) for seizures > 5 min	✓ Rule out Symptomatic Seizures ✓ Start AEDs even if the first seizure

▪ **For symptomatic seizures:**

Treat the underlying cause (hypoglycemia, urea cycle abnormality, meningitis, temporal lobe tumor, etc.)

▪ **Educating the family and the child about**

- The disease, and its management
- How to handle seizures acutely and use of rescue medications
- Watch the child during swimming in pools, passing traffic,
- Never to stop the AEDs suddenly
- Exercise: can share in hockey, baseball, basketball, and football

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▪ **Anti-epileptic drugs (AEDs)**

How to start?

- Choice should be based on the type of seizure and the epilepsy syndrome
- Only **one** drug is used with small dose → if no response → gradually increase the dose.
- Control with 1 drug (monotherapy) should be the goal
- In resistant cases a **2nd** drug can be used alone or in combination.

When to stop?

- Children are free of seizures for at least 2 yr with normal EEG at discontinuation
- AED therapy should be discontinued gradually, over a period of 3-6 mo

Disorder	Drug of first choice
– Focal – Secondary generalized seizures	▪ Oxcarbazepine, levetiracetam, carbamazepine
– Absence seizures	▪ Ethosuximide (Zarontin) ▪ Treatment is guided by EEG
– Both absence & generalized motor seizures coexist – Generalized epilepsies	▪ Valproate /Lamotrigine
– Myoclonic epilepsy	▪ Valproate/ Lamotrigine
– Infantile spasms	▪ Adrenocorticotrophic hormone (ACTH) <ul style="list-style-type: none"> – Suppresses the expression of corticotrophin-releasing hormone, a proconvulsant neuropeptide whose expression may be enhanced in patients with infantile spasms – Intramuscular or Gel in a tapering doses – Monitor the patient's response with serial EEG ▪ Vigabatrin (Sabril) ; retinal toxicity is a risk
– Migraine and epilepsy	Valproate or Topiramate (effective in both)

Other new FDA approved anti-epileptic medications e.g.

- Perampanel (Fycompa)
- Rufinamide (Banzel)
- Clobazam (Onfi)

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	Na valproate	Carbamazepine	Levetiracetam	Lamotrigine
Dose	20-40 mg/kg/d	10-20 mg/kg/d	20-40 mg/kg/d	1-15 mg/kg/d
Side effect	<ul style="list-style-type: none"> – Sedation – Hepatotoxic – Alopecia – Weight gain 	<ul style="list-style-type: none"> – Sedation – Hepatotoxic – Anemia – Leucopenia 	<ul style="list-style-type: none"> – Somnolence – Asthenia – Behavioral disorders 	<ul style="list-style-type: none"> – Dizziness – Headache, ataxia – Stevens-Johnson syndrome

▪ **Ketogenic diet:**

- For infants < 2year with resistant myoclonic epilepsy
- Most calories given form fat (never used with valproate)

Differential diagnosis: from conditions mimic epilepsy

1. Vagal syncope

- Triggered by sight of blood, pain, or sudden stress
- There is initially pallor and sweating followed by blurring of vision, dizziness, nausea, and then gradual collapse with loss of consciousness
- Rapid recovery with no postictal depression
- If prolonged ; lead to generalized convulsions, termed anoxic seizures

2. Cardiac syncope:

- Long QT syndromes
- Aortic stenosis

Syncope mostly predisposed by Exercise

3. Breath holding attacks

- Episode starts with a cry (often a “silent” cry and marked pallor in the case of the pallid type), and progresses to apnea and cyanosis.
- Spells usually begin between 6 and 18 mo of age.
- Syncope, tonic posturing, and even reflex anoxic seizures
- Association iron deficiency anemia is common

4. Psychogenic nonepileptic seizures

- Predisposed by stress
- Gradual onset
- Asynchronous flailing limb movements that vary between attacks
- No injury, closed eyelids
- May respond to suggestion during “loss of consciousness”
- Usually >2-3 min

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Status Epilepticus

Definition

- Continuous seizure activity or recurrent seizure activity without regaining of consciousness lasting for >30 min
- Impending status epilepticus: seizures lasting between 5 and 30 min

Etiology

1. Prolonged febrile seizures (the commonest cause)
2. Sudden withdrawal of anticonvulsants in an epileptic patient
3. CNS anomalies or infections (e.g. encephalitis) or tumors.
4. Metabolic disorders e.g. hypoglycemia, inborn errors of metabolism

Clinical types

- Convulsive status epilepticus (generalized tonic, clonic, or tonic-clonic)
- Nonconvulsive status (complex partial, absence)
- Myoclonic status

Management

A. Initial assessment

- A brief physical examination should assess respiratory and circulatory status.
- A rapid neurologic examination provides a preliminary classification of the type of status epilepticus.
- A history from a parent or caregiver for possible cause of the seizures.

B. Initial intervention:

In the first 5 minutes of seizure activity

a) Airway	<ul style="list-style-type: none"> – Maintain airway. – Suction of secretions
b) Breathing	<ul style="list-style-type: none"> – O₂ inhalation – Assisted ventilation
c) Circulation	<ul style="list-style-type: none"> – Secure an I.V. line
d) Draw Samples for	<ul style="list-style-type: none"> – Electrolytes, Glucose, Calcium and magnesium – Basic metabolic panel for inborn errors of metabolism – Culture blood and CSF – Toxic screen – AEDs level in known epileptics
e) Continuous EEG	<ul style="list-style-type: none"> – Helps diagnosis – Monitor response to treatment
f) Glucose 10% 5ml/Kg For hypoglycemia	

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C. Control convulsions**Emergent therapy (6-15 minutes)**

IV line available	<p>I.V slow Lorazepam (0.05mg/kg) May be repeat in 5-10 minutes</p> <p>or</p> <p>Diazepam (0.3mg/kg) May be repeat in 5-10 minutes</p> <p>or</p> <p>Midazolam (0.2 mg/kg) Followed by IV infusion (With all benzodiazepines ; monitor and manage respiratory depression)</p>
IV line un available	<p>Buccal or intranasal midazolam</p> <p>or</p> <p>Intranasal lorazepam</p> <p>or</p> <p>Rectal diazepam are effective options</p>

Urgent therapy (16-35 minutes)

- Give immediately Phosphenytion or phenytion
 - Loading 15-20 mg/kg under ECG monitor
 - Not > 0.5-1 mg/kg/min
 - Take peak blood level 2 hr later
 - Maintain on 3-6 mg/kg/24 hr
- Phenobarbitone is often the next medication at a loading dose of 5-10 mg/kg
- IV Valproate (25mg/kg) is emerging as a strong evidence urgent therapy

If seizures controlled	Refractory status epilepticus
Use maintenance doses of phenytion and /or phenobarbitone	<ul style="list-style-type: none"> ▪ Intubate and assist respiration ▪ Drug options: <ul style="list-style-type: none"> – Midazolam infusion – Propfol infusion – Barbiturate coma – General anesthesia ▪ Careful attention to blood pressure ▪ Monitor response with EEG

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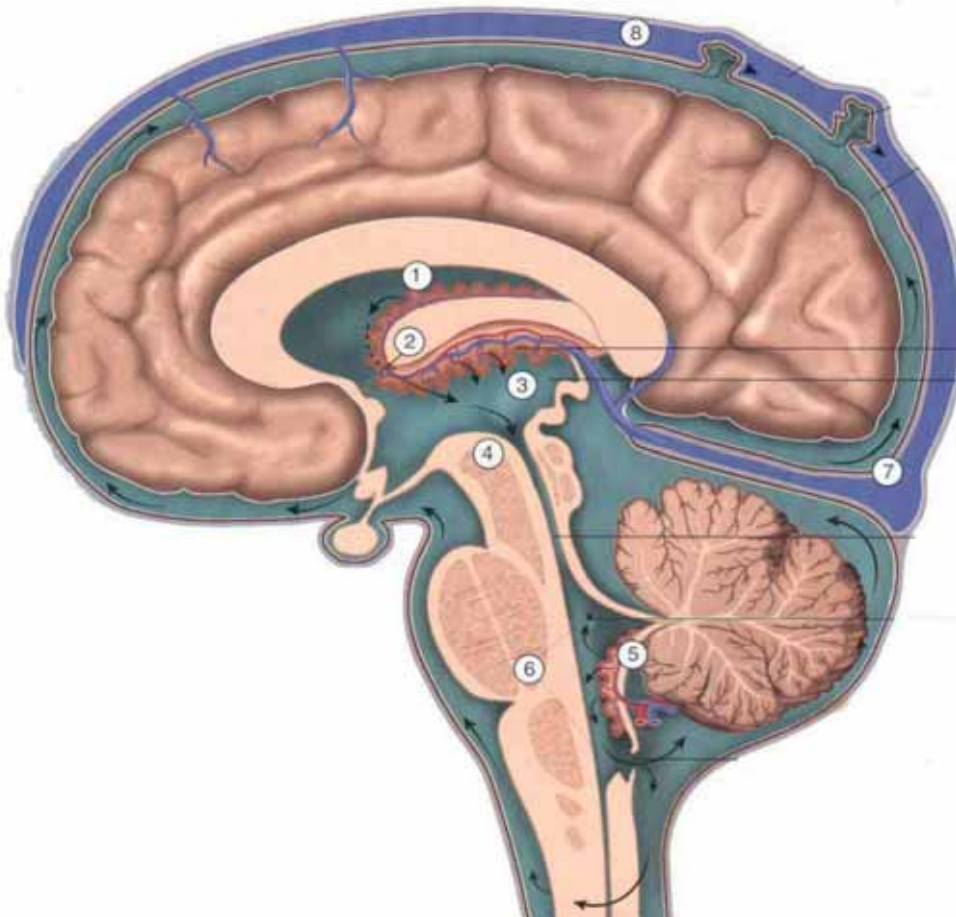
Hydrocephalus

Definition

- Excessive accumulation of CSF with enlargement of cerebral ventricles with or without increase of the intra cranial pressure; ICP
- Hydrocephalus is not a specific disease; it represents a diverse group of conditions that result mainly from impaired circulation and/or absorption of CSF .

Normal CSF circulation:

CSF amount in infant = **50** ml (150 in adult)



1. CSF is formed by active secretion by choroids plexus mainly in the lateral ventricles
2. CSF passes via foramen of Monro to the 3rd ventricle
4. Then via aqueduct of Sylvius to the 4th ventricle
5. Then via foramina of Luschka & Magendie to the subarachnoid space
7. CSF in subarachnoid space is absorbed by arachnoid villi to dural venous sinuses

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Causes of hydrocephalus

I. Relative hydrocephalus: Normotensive hydrocephalus

- Apparent increase in CSF due to brain atrophy
- Not associated with raised ICP

II. Absolute hydrocephalus

A. Obstructive hydrocephalus

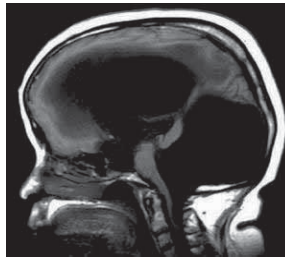
Obstructed CSF flow within the ventricular system (Non-communicating)

1. Obstruction of aqueduct of Silvius:

- * Congenital atresia:
 - May be sex linked recessive.
 - May be associated with spina bifida occulta
- * Obstruction from outside by:
 - Brain tumors.
 - Malformation of vein of Galen (listen for A cranial bruit).
- * Obstruction from inside:
 - Post hemorrhagic (especially in premature).
 - Post meningitis (T.B., pneumococci, mumps)

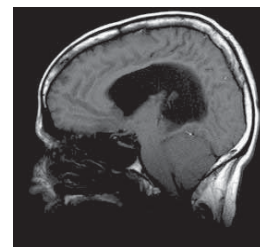
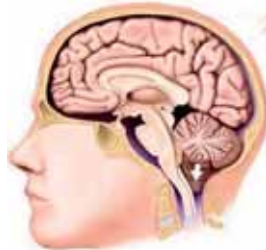
2. Congenital atresia of:

- * Foramen of Monro.
- * Foramina of Luschka & Magendi: Cystic dilatation of 4th ventricle usually with cerebellar vermis agenesis (**Dandy Walker malformation**)



3. Arnold Chiari malformation:

Congenital downward displacement of cerebellum, pons & medulla



4. Congenital infection especially toxoplasmosis

5. Brain tumors

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B. Non obstructive hydrocephalus (Communicating) due to either:

1. Defective CSF absorption

- * Subarachnoid space adhesions: - Post hemorrhagic or post meningitic
- * Leukemic infiltration.
- * Dural sinus thrombosis

2. Excessive CSF secretion (Rare) due to:

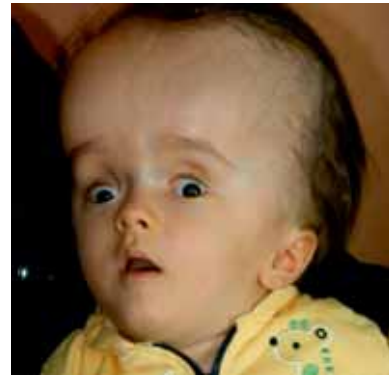
- Choroid plexus papilloma
- Choroid plexus congestion as in meningitis

Clinical picture

In infant

1. Head signs

Marked; as the cranial sutures are still opened and yield under rising ICP



- Accelerated rate of enlargement of the head is the most prominent sign. (increasing head circumference on serial measurements)
- Fontanels are widely opened & bulging.
- Sutures are widely separated.
- Dilated scalp veins.
- Eyes deviated downwards → Sunset appearance
- Skull percussion → Cracked pot sound (Macewen sign).
- Craniotabes in all bones
- A foreshortened occiput suggests Chiari malformation, and a prominent occiput suggests the Dandy-Walker malformation.

2. Neurologic signs

Mild, as rapid ↑ in skull size protect against marked increase of ICP

- Mild vomiting
- Squint
- Delayed motor milestones
- Pyramidal tract lesion signs are common especially in lower limbs.
- In advanced cases: mental retardation & optic atrophy may occur.

In older child

Marked neurologic manifestations as the sutures are not easily separated with subsequent marked increase ICP

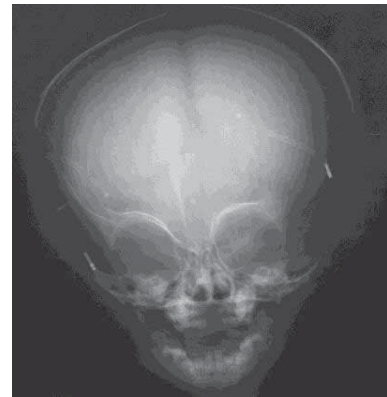
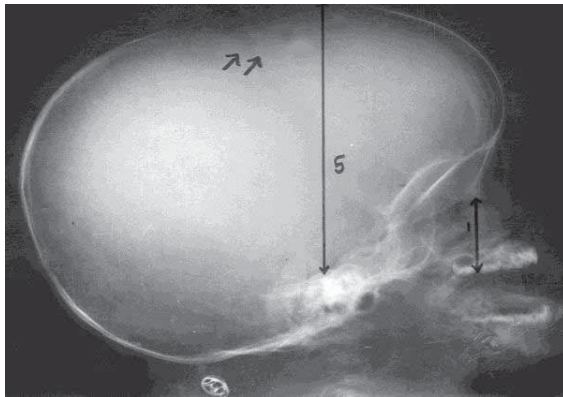
- Bursting headache; severe in the morning
- Blur of vision
- Projectile vomiting (unrelated to meals, not preceded by nausea)
- Bradycardia & hypertension (Cushing response)

Diagnosis**A. Confirm hydrocephalus**

1. Clinical picture: Progressive head enlargement on serial measurements

2. Cranial X-ray

A. Before closure of sutures and fontanel:



- Wide fontanel, wide separation of sutures.
- Craniofacial disproportion with large cranium.

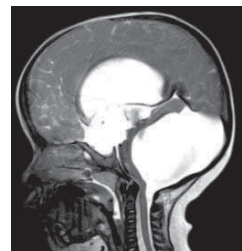
B. After closure of sutures and fontanel:



- Increased ICP (beaten silver appearance, wide sella)

3. Trans fontanel cranial ultrasound**4. CT & MRI**

- Diagnostic; can detect ventricular dilatation.
- Detect degree of cortical atrophy.
- May detect the cause



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B. Type of hydrocephalus; obstructive or communicating?

1. CT & MRI: The most accurate and non-invasive ✓✓
2. Simultaneous lumbar & ventricular manometry:
 - Normally, both are equal
 - Ventricular pressure > spinal pressure in obstructive hydrocephalus
3. CSF examination: xanthochromia & cytoalbuminous dissociation in obstructive type

N.B: Examination of fundus is mandatory for:

- Evidence of chorioretinitis in congenital infections e.g. toxoplasmosis
- Check for papilledema in older child

Treatment**Medical**

Decrease CSF by:

- Carbonic anhydrase inhibitors; acetazolamide (Diamox tablets)
- Furosemide

For:

- Moderate or slowly progressive ventricular dilatation
- If response is not stable → proceed to shunt operation

Draw backs:

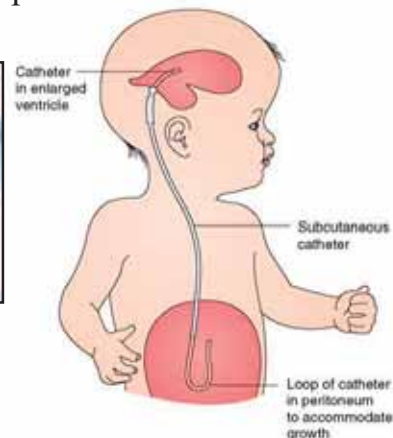
- Transient effect
- Electrolyte & pH disturbances

Surgical

1. Choroid plexectomy **or** diathermy for choroid papilloma
2. Extra cranial shunt operation

Types

- Ventriculoperitoneal →
- Ventriculo artial (right)
- Ventriculopleural

**Complications**

- Shunt nephritis (immune complex mediated)
- Obstruction (headache, papilledema, emesis, mental status changes)
- Infection commonly with staph epidermidis (fever, headache, meningismus)
- Relative shortening as the child grow

Differential diagnosis macrocephaly

From causes of **macrocephaly** (H.C > 2 standard deviation above mean)

Cranial causes

- Constitutional
- Achondroplasia
- Familial
- Anemia (chronic hemolytic)
- Rickets

Intracranial causes

- Hydrocephalus
- Hydrancephaly
- Space occupying lesion e.g. tumor
- Megalencephaly which may be due to:
 - Cretinism
 - Storage diseases (e.g. mucopolysaccharidosis).
 - Familial

Microcephaly

Definition: Head circumference measures > 3 SD below the mean for age and sex

Causes

- 1- True microcephaly due to small sized brain.
- 2- Craniosynostosis due to early fusion of sutures.

i. True microcephaly

Criteria

- Skull sutures & fontanelles → normal.
- No increase intra cranial tension.
- Skull X ray show small vault.
- CT scan shows brain atrophy.

Etiology

a. Genetic

- Familial → AR, (severe atrophy of frontal lobes → camel head)
- Chromosomal syndromes e.g. trisomy 21, 18, 13

b. Secondary (Non genetic)

- * Prenatal:
 - TORCH infection.
 - Fetal irradiation; especially in the 2nd trimester.
 - Maternal diabetes or phenyle ketonuria.
 - Maternal drugs e.g. phenytoin, & alcohol.
- * Natal: Hypoxic ischemic encephalopathy.
- * Post-natal: Early meningitis & Encephalitis

ii. Craniosynostosis

Definition: early fusion of skull sutures;

1. Palpable ridge is felt at the affected suture.
2. If multiple sutures are affected:
 - Microcephaly → brain atrophy.
 - Increase intra cranial tension → hydrocephalus & beaten silver appearance in skull X ray.
3. Skull examination → abnormal skull shape which may be:
 - a. Scaphocephaly (Dolicocephaly)**
 - Elongated due to premature closure of sagittal suture



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b. Brachycephaly

- Short anteroposterior
- Due to bilateral closure of coronal sutures

**c. Oxycephaly**

- Conical head
- Due to multiple sutures closure

**d. Trigonocephaly**

- Triangular
- Due to closure of metopic suture

**Treatment**

Surgical separation of skull sutures is indicated in:

- Cases with hydrocephalus.
- Cases with progressively increase intra cranial tension.
- Cosmotic reasons.

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Cerebral Palsy

(Little's Disease)

Definition

- A group of permanent disorders of movement and posture causing activity limitation
- Resulting from non-progressive lesions to the developing fetal or infant brain
- Affecting mainly the motor centers; cerebral cortex , cerebellum , and basal ganglia
- With frequent neurologic associations including:
 - Mental retardation
 - Epilepsy
 - Impaired hearing ;deafness
 - Impaired vision
 - Emotional disturbances
 - Behavioral disturbances

Causes

- **Pre-natal (80%)**
 - Antenatal Infections
 - Congenital malformations
 - Fetal asphyxia
- **Natal (10%)**
 - Birth asphyxia
 - Birth trauma
- **Post-natal (10%)**
 - VLBW with intracranial hemorrhage
 - Meningitis, encephalitis
 - Metabolic e.g. phenyle ketonuria
 - Hypoglycemia
 - Hyper bilirubinemia
 - Hydrocephalus.

Topographic classification: (distribution of motor defect)

- 1- Monoplegia → Only one limb is affected
- 2- Hemiplegia → Upper and lower limbs on one side are affected
- 3- Diplegia → All limbs are affected, the lower more affected than the upper limbs
- 4- Paraplegia → Only both lower limbs are affected
- 5- Quadriplegia → All the four limbs are affected

Clinical Types

1. Spastic cerebral palsy

Criteria

- The commonest type
- Pyramidal tract lesion (UMNL) signs:
 - Hypertonia
 - Hyper reflexia
 - Positive Babinski sign
 - May be clonus
- Persistence of primitive reflexes
- Pesudobulbar palsy → feeding disorder (poor suckling & swallowing), squint and speech disorders.

Types

1. **Spastic diplegia: 35%**

- Bilateral spasticity of the legs that is greater than in the arms
- More in premature with periventricular leucomalacia
 - Crawling is commando like rather than four limbed crawling.
 - Lower limbs scissoring (application of a diaper is difficult)
 - With paraspinal muscle involvement, the child may be unable to sit.
- MRI typically shows scarring and shrinkage in the periventricular white matter with compensatory enlargement of the cerebral ventricles

2. **Spastic hemiplegia: 25%**

- Due to in utero or neonatal stroke
 - Decreased spontaneous movements on the affected side
 - Shows hand preference at a very early age
 - Walking is delayed until 18-24 mo (tiptoe walking); gait is circumdactive
 - Examination of the extremities may show growth arrest, particularly in the hand and thumbnail
 - Upper extremity assumes a flexed posture when the child runs

3. **Spastic quadriplegia: 20%**

- More ischemia and infection
- The most severe type
- Marked motor impairment of all extremities and the high association with mental retardation and seizures

4. **Spastic monoplegia**

5. **Spastic paraplegia**

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2. Ataxic cerebral palsy**Criteria**

- Hypotonia and hyporeflexia
- Cerebellar ataxia → incoordination of voluntary movements, nystagmus, staccato speech, intention tremors.

3. Extrapyramidal (dyskinetic, athetoid) cerebral palsy**Commonest causes**

- Asphyxia, kernicterus

Criteria

- Hypotonia (replaced with time with hypertonia & rigidity)
- Chorio athetoid movements.
- Deafness.

3. Atonic cerebral palsy

- Profound hypotonia → floppy infant
- Preserved deep tendon reflexes

5. Mixed cerebral palsy**Diagnosis**

1. Clinical: A thorough history and physical examination should rule out a progressive disorder of the CNS, including degenerative diseases, metabolic disorders, spinal cord tumor, or muscular dystrophy
2. Investigations:
 - Value: Exclude progressive brain insults and may detect a cause or association
 - a. CT & MRI
 - May detect the cause e.g. brain malformations and spinal cord lesions
 - Rule out brain tumors & degenerative brain disease.
 - CT scan may be useful for detecting calcifications associated with congenital infections
 - b. TORCH screen.
 - c. Genetic evaluation
 - d. Metabolic screen.
 - e. For associations: Test for Hearing, Visual function , EEG for seizures

N.B Conditions that can mimic cerebral palsy

- Spinal cord tumors
- Channelopathies
- Sandifer syndrome
- MECP2 duplication
- Congenital dopa-responsive disorders
- Genetic spastic paraplegia
- Some metabolic conditions (GLUT1 deficiency, glutaric aciduria type 1)
- Ataxia telangiectasia

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Treatment

- Multidisciplinary approach is most helpful in the assessment and treatment of such children; A team of physicians from various specialties as:
 - Occupational and physical therapists
 - Speech pathologists
 - Social workers
 - Educators
 - Developmental psychologists
- **Assist:**
 - Feeding & defecation
 - Vision and hearing
 - Walking: Walkers, standing frames, motorized wheel chair
 - Communication by talking typewriters and special computers
 - Rehabilitation according to the degree of motor disability

▪ **Medications**

Anti spastic drugs

drug	Action	Side effect
Diazepam	<ul style="list-style-type: none"> – GABA agonist – Useful in short term relief of painful spasms 	<ul style="list-style-type: none"> – Sedation – Dependency with long term use
Baclofen	<ul style="list-style-type: none"> – GABA agonist and inhibit spinal neuronal transmission – When used intrathecally, via a surgically implanted continuous-delivery pump → greater efficacy with fewer adverse effects 	<ul style="list-style-type: none"> – Sedation
Tizanidine	<ul style="list-style-type: none"> – Alpha-2 adrenergic receptor agonist and inhibit spinal neuronal transmission – Useful in severely disabled by cerebral palsy and in those with night-time spasms 	<ul style="list-style-type: none"> – Sedation
Dantrolene	<ul style="list-style-type: none"> – Block calcium intake by skeletal muscles → ↓ free intracellular calcium 	<ul style="list-style-type: none"> – Hepatic dysfunction – Blood dyscrasia

Botox A: injection in spastic muscles and salivary glands to reduce drooling. It stops the release of acetylcholine at the synapse and blocks neurotransmission. The effects gradually wear off (over about 3–6 months)

Levodopa: Small doses may be helpful for dystonia and rigidity

▪ **Surgery:**

For marked spasticity of the lower extremities → surgical soft tissue procedures that reduce muscle spasm e.g. adductor tenotomy or psoas transfer and rhizotomy (roots of the spinal nerves are divided)

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Mental Retardation

Definition: Handicapping disorder with age of onset below 18 years characterized By subnormal I.Q. (< 70%).

$$\text{I.Q. (Intelligence Quotient)} = \frac{\text{Mental age}}{\text{Chronological age}} \times 100$$

Diagnostic criteria

- 1- Subnormal intelligence quotient "IQ" (less than or equal to 70%)
- 2- Limitations exist in two or more of the adaptive skills e.g. communications, social skills, self care, safety, functional academics, work
- 3- Manifest before age of 18 years (if after 18 years, it is called dementia.)

Etiology

1. Physiologic (sub cultural)

- No demonstrable organic brain lesions
- Seen in children living in low socio economic standard with neglect and poverty

2. Genetic causes

- Chromosomal anomalies; e.g. Trisomy 21,18,13, klinefelter syndrome
- Genetic disorders e.g. Fragile-X syndrome , prader willi syndrome
- Developmental brain abnormalities e.g. hydrocephalus and familial microcephaly
- Degenerative brain diseases e.g. lipidosis and mucopolysacridosis
- Inborn errors of metabolism

2. Non genetic

- Cerebral palsy causes (**Mention**)
- Congenital hypothyroidism
- Severe hypernatremia or recurrent hypoglycemia

Presentations

Age	Manifestation
Infancy	<ul style="list-style-type: none"> – Delayed social development → Fail to interact with environment – Gross motor delay
Early childhood	<ul style="list-style-type: none"> – Language delay /difficulties – Behavior difficulties – Delayed fine motor
Late childhood	<ul style="list-style-type: none"> – Academic under achievement

Prevention

- Proper prenatal, natal and post-natal care
- Vaccination against rubella for females (not during pregnancy)

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- Neonatal screening to identify preventable causes of MR (e.g. phenylketonuria).
- Treatment of neonatal jaundice, hypoglycemia, hypothyroidism

Evaluation:

1. Neuro imaging → CT , MRI
2. T4 ,TSH
3. Karyotyping
4. Fragile X screen
5. Metabolic → e.g. plasma amino acids , urine organic acids , ...

Treatment

Only rehabilitation of the child depending on the degree of mental retardation:

- Mild (IQ 50-70) → educable (may need special classes)
- Moderate (IQ 35-50) → trainable (they are trained to care for themselves)
- Severe (IQ 20-35) → ± trainable.
- Profound (IQ 0-20) → non trainable (so, they need full time nursing care).

Acute post infectious polyneuropathy (Gillian Barre syndrome)

Etiology

- Auto immune, often postinfectious polyneuropathy involving mainly motor but also sensory and sometimes autonomic nerves
- Paralysis usually follows a nonspecific gastrointestinal (especially *Campylobacter jejuni*, or *Helicobacter pylori*) or respiratory infection (especially *Mycoplasma pneumonia*) or viral infections.

Clinical picture

1. Motor : Acute ascending flaccid paralysis:

Criteria:

- Bilateral & symmetric usually (asymmetric in 9%)
- Associated hypotonia & hyporeflexia.

Progress:

- Lower Limb (inability or refusal to walk) → trunk → upper limb.
- Bulbar palsy (in 50%) → dysphonia, dysphagia & lost bulbar reflexes.
- Respiratory muscles → respiratory failure.
- ✓ **Miller-Fisher syndrome** consists of acute external ophthalmoplegia, ataxia, and areflexia

2. Sensory

- Mild
- Tender calf

3. Autonomic

- Labile blood pressure & heart rate
- Urinary incontinence or retention of urine in about 20%

Diagnosis

✓ **CSF:** Cyto albuminous dissociation :

- High CSF protein > twice the upper limit of normal and a lack of cellular response < 10 white blood cells/mm³
- Negative bacterial culture

✓ **MRI of the spinal cord**

- Thickening of the cauda equina and intrathecal nerve roots in >90% of patients
- Rule out other spinal disorders

- Motor nerve conduction velocity are greatly reduced
- Electromyography shows evidence of acute denervation of muscle.
- Serum creatine kinase (CK) level may be mildly elevated or normal

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Treatment

Patients in early stages of this acute disease should be admitted to the hospital for observation because the ascending paralysis can rapidly involve respiratory muscles during the next 24 hr

i. Supportive:

- Respiratory effort monitoring (spirometry) and support
- Cardiac monitoring
- Nasogastric feeding
- Care of bladder (catheterization & neostigmine).
- Physiotherapy

ii. Specific

- IVIG: A commonly recommended protocol is IVIG 0.4 g/kg/day for 5 consecutive days, but some studies suggest that larger doses are more effective (1 g/kg/day for 2 consecutive days)
- Alternatives: if IVIG is ineffective
 - Plasmapheresis is equally effective as IVIG.
 - Combined IVIG and interferon is effective in some patients
 - Steroids are not effective

Differential diagnosis: Other causes of acute flaccid paralysis

Prognosis

- The clinical course is usually benign, and spontaneous recovery begins within 2-3 wk.
- Most patients regain full muscular strength, although some are left with residual weakness.
- Improvement usually follows a gradient opposite the direction of involvement: bulbar function recovering first, and lower extremity weakness resolving last.

Differential diagnosis : Acute Flaccid Paralysis

A. Acute asymmetrical paralysis

- Cerebrovascular stroke e.g. acute hemiplegia
- Poliomyelitis
- Pseudo paralysis e.g. with osteomyelitis, trauma, scurvy

B. Acute symmetrical paralysis

- * Spinal cord: Trauma, Compression by abscess or tumors, Transverse myelitis
- * Infections: Botulism, Diphtheria, Rabies
- * Post infections: Guillain Barre syndrome, Enterovirus Associated Post Infectious Myelitis (*Recently discovered in USA*)
- * Tick-bite paralysis
- * Myasthenia gravis
- * Hypokalemic periodic paralysis

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Inability To Walk

Normal walking require integration between CNS, muscles, skeleton and training

Causes of delayed walking

A. Central causes:

1-Brain	<ul style="list-style-type: none"> - Cerebral palsy - Mental retardation - Hydrocephalus - Congenital malformations - Brain damage with tumors or infections
2- Spinal cord	<ul style="list-style-type: none"> - Congenital→ Spina bifida. - Traumatic→ Spinal cord trauma. - Inflammatory→ Pott's disease of the spine. - Neoplastic→ Spinal cord tumors.
3- Anterior horn cells	<ul style="list-style-type: none"> - Poliomyelitis. - Spinal muscle atrophy.(Werdnig Hoffman disease)
4- Peripheral Nerve	<ul style="list-style-type: none"> - Guillian - Barre syndrome.. - Polyneuritis (Diphtheria, Drugs)
5- Neuro muscular junction	<ul style="list-style-type: none"> - Myasthenia gravis. - Botulism - Organophosphorus poisoning.

B. Muscular causes:

* Primary muscle disorders: Myopathies, Myositis and Metabolic.

* Secondary muscle disorders: Rickets and malnutrition.

C. Skeletal: (Bones, Joints)

- Rickets
- Inflammation (arthritis, osteomyelitis)
- Lower limb trauma

Differential diagnosis of inability to walk:

Causes	Primary (The child has not walked before)	Secondary (The child has walked before)
a.Paralytic	<ul style="list-style-type: none"> - Early poliomyelitis. - Early paralysis before walking. - Cerebral palsy 	<ul style="list-style-type: none"> - Poliomyelitis. - Post diphtheric paralysis - Post encephalitic paralysis - Cerebro-vascular accidents
b.Non paralytic	<ul style="list-style-type: none"> - Rickets - Mental retardation - Simple delayed walking 	<ul style="list-style-type: none"> - Rickets. - Malnutrition. - Fractures or osteomyelitis

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الدفعۃ ال14

Illustrated Baby Nelson

General Pediatrics



By

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Dedication

To all who inspired me

My mother and father

My wife and kids

To the souls of My father in law; ~~Dr Ahmed Hamdi Elwelili~~ and my mother in law

And To my professors:

Dr ~~Mohamed Hamza Sayed Al Ahl~~

Dr ~~Aly Mohamed Abu Zeid~~

Dr ~~Mostafa fathy~~

And the souls of my friends; Dr ~~Wael Assal~~ and Dr ~~Osama Al Sayed~~

For all I must say: Thank You

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Mohamed El Koumi

October 6 city

7th of March 2017

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Growth and development

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الدفعۃ ال14

Factors affecting growth

1. Prenatal factors

- Familial (genetic); children inherit their height pattern from their parents
- Racial; some races are shorter than others e.g. Chinese
- Constitutional

2. Factors operating during pregnancy (In Utero Exposures)

- Maternal diseases e.g. diabetes mellitus, hypertension
- Maternal exposures: Teratogens, infections e.g. TORCH, irradiations...
- Maternal nutritional state.

3. After birth

- a. Age: Growth rate is more during infancy and adolescence.
- b. Sex:
 - Growth rate is nearly equal in males & females from birth till 11 years
 - Girls grow faster between 11 – 14 years (due to earlier puberty)
 - Boys grow faster than girls beyond 14 years (due to later puberty)
- c. Nutritional status → Chronic under nutrition & malnutrition retard growth
- d. Psychological and socioeconomic status
- e. Health status → chronic diseases retard growth

4. Hormonal role: growth is controlled by hormones depending on the stage

Intrauterine	Infancy & childhood	Adolescence
1. Chorionic gonadotropines 2. Placental lactogen 3. Insulin 4. Thyroxin (skeletal growth)	1. Thyroxin 2. Growth hormone	Sex hormones (Estrogen & androgen) are responsible for growth spurt during puberty

So

- Newborn of diabetic mother whose mother has hyperglycemia during pregnancy commonly have hyperinsulinemia and eventual macrosomia at birth
- Newborn with congenital hypothyroidism usually has delayed bone age screened for by plain radiograph on his knee that shows absent tibial and femoral epiphyseal centers that normally present at birth
- Newborn with growth hormone deficiency usually has normal size at birth simply because growth hormone actions operate after birth onwards

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I. Anthropometric measures

1. Weight

- * At birth → 3 - 3.5 kg
- * During the 1st year:
 - 1st 4 months → Weight ↑ by $\frac{3}{4}$ kg per month.
So, weight at 4 months = 6 kg ⇒ double birth weight
 - Next 4 months → Weight ↑ by $\frac{1}{2}$ kg per month
 - Last 4 months → Weight ↑ by $\frac{1}{4}$ kg per month.
So, weight at 1 year = 9 kg ⇒ triple birth weight
- * Beyond the 1st year → Weight is calculated as: **weight = age (in years) × 2 + 8**

Physiologic weight loss:

- * Initial weight loss usually occur during the first 3-4 days of life
- * The baby loses about 10% of his birth weight due to:
 - Scanty milk flow
 - Poor suckling capacity
 - Passage of meconium & urine
- * This weight loss is usually regained by the 10th day of life

2. Length/Height

* At birth	→	50 cm
* At 6 months	→	68 cm
* At 1 year	→	75 cm
* At 2 years	→	87.5 cm
* After the 2 nd year	→	Height = age in years × 5 + 80



How to measure?

- Under 2 years: Length is measured in supine position
- Over 2 years: Height is measured in standing position

3. Occipito Frontal head circumference (OFC)

Clinical value

- OFC reflects the rate of brain growth.
- Maximum rate of brain growth & OFC is during the 1st year

* At birth	→	35 cm.
* At 6 month	→	43 cm
* At 1 year	→	45 cm
* At 12 years	→	55 cm



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4. OFC & chest circumference (CC) ratio

Chest circumference is measured at level of xiphoid process in mid inspiration

Age	OFC/CC ratio
* At birth	> 1
* At 6 months	Equal 1
* at 1 year	< 1
* At 5 th year	< 1

Clinical value: Suspect malnutrition if OFC/C.C > 1 beyond 6 months

5. Mid arm circumference (MAC)

* In a baby 1- 4 years	→	MAC is > 14 cm
* In border line malnutrition	→	MAC is 12 – 14 cm
* In severe malnutrition	→	MAC is < 12.5 cm



Clinical value

- Early indicator of malnutrition; and is not affected by edema.
- Often used for screening for malnutrition in lieu of weight for height
- MUAC divided by OFC classifies malnutrition into; Mild < 0.31 , moderate < 0.28 , and severe < 0.25 (*Kanawati classification of malnutrition*)

6. Skin fold thickness

Clinical value: Estimate total body fat;

- * Measured by skin fold calipers
- * Measured at left triceps or left subscapular regions
- * Normal values: - 10 mm at 1 year
- 14 mm at 1- 4 years



8. The Arm span - Height relationship

- * Span is shorter than height by 3 cm at 1-7 years.
- * Span equals height at 8-12 years.

7. Proportions of upper segment & lower segment

- * Upper segment (US) is measured from crown to symphysis pubis.
- * Lower segment (LS) is measured from symphysis pubis to the floor.
- * Proportions of US/LS:
 - At birth → 1.7 /1
 - At 3 years → 1.3 /1
 - After 7 years → 1 /1

Clinical value: Help evaluation of short stature

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II. Teething

Primary = Deciduous or Milky teeth		Secondary (permanent) Teeth	
Tooth	Age (months)	Tooth	Age (years)
- Central incisor	6 - 9	- Central incisor	7
- Lateral incisor	9 - 12	- Lateral incisor	8
- 1 st molar	12- 18	- Canine	10
- Canine	18- 24	- 1 st premolar	11
- 2 nd molar	24	- 2 nd premolar	12
		- 1st molar	6
		- 2 nd molar	13
		- Wisdom tooth	22
* Count : 20 teeth * Teething starts at 6- 9 months and completed at 24 months. * The lower jaw incisors precedes the upper jaw by one month		* Count : 32 teeth * Teething start at the 6 th years and completed at 22 nd years * Eruption follow exfoliation immediate or may lag 4-5 months	

Teething Eruption Abnormalities

1. Delayed teething: No eruption beyond 13 months of age.

Causes :

- a. Idiopathic : the commonest cause
- b. Local: e.g. supernumerary tooth, cysts, rigid gums
- c. Generalized: (DACRO H2); Down syndrome, Achondroplasia, Congenital hypothyroidism, Rickets, Osteogenesis imperfecta, Hypopituitarism, Hypoparathyroidism

2. Premature teething is seen is:

- Natal teeth (should be extracted to avoid aspiration).
- Congenital syphilis
- **Ellis Van Creveld syndrome:**
 - Disproportionate dwarfism (short stature with short limbs)
 - Post axial polydactyly
 - Ectodermal dysplasia (teeth and nail)
 - Congenital heart disease (ASD)
 - Narrow chest



3. Congenital missing or extra tooth

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III. Fontanels

Posterior fontanel

- ⊕ Normally: Closed at birth or opened < 0.5 cm and closes within 2 months
- ⊕ Abnormally: Opened > 1 cm or Not closed within 4 months

Causes :

- Prematurity
- Increased intra cranial tension
- Mongolism
- Cretinism

Anterior fontanel: Clinical value

1. Assessment of growth

- At birth \rightarrow 3 fingers ($\approx 3-4$ cm).
- At 6 months \rightarrow 2 fingers.
- At 12 months \rightarrow 1 finger.
- At 18 months \rightarrow closed.

2. Size

A- Large fontanel (delayed closure) in: (DACRO HI)

- Down syndrome
- Achondroplasia
- Congenital hypothyroidism
- Rickets
- Osteogenesis imperfecta
- Hypopituitarism
- Increased intra cranial tension

B- Small fontanel (premature closure; before 6 months) in: (2 C)

- Craniosynostosis
- Congenital hyperthyroidism

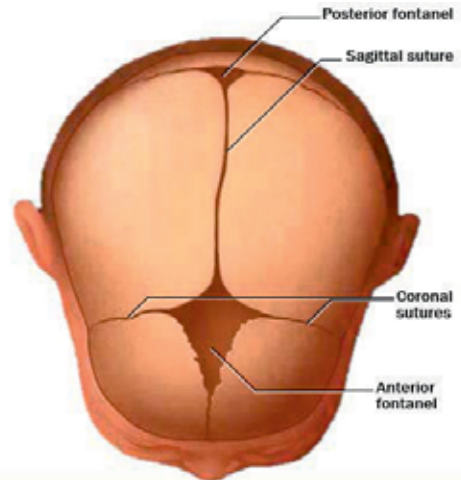
3. Surface : Normally it is smooth & continuous with the skull bones.

A- Bulging: with \uparrow intra cranial tension e.g.

- Intra cranial infections
- Hydrocephalus
- Intra cranial hemorrhage



B- Depressed : in dehydration



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IV. Osseous Growth

Normally; there are 5 secondary ossific centers at birth in

- Lower end of femur.
- Upper end of tibia.
- Calcaneus, talus & cuboid

“X ray knee in newborn help assess intrauterine skeletal maturation ; it is a good screening tool for congenital hypothyroidism”



Carpal bones start ossification after birth as follow

- The 1st carpal bone → ossifies at about 2nd month of age.
- The 2nd carpal bone → ossifies by the end of the first year.
- Later on, one carpal bone ossifies approximately each year till the 6th year; the 8th bone usually ossifies at the 12th year of age.

Bone age

- Bone age is a measure of the degree of skeletal maturity of a child
- It is measured in years by the radiographic examination of ossification centers; most often using the Greulich-Pyle bone age scale
 - At > 6 month onwards → by x-ray over the left wrist
 - In late childhood → by assessing fusion of epiphysis

Causes of Delayed Bone Age	Causes of Advanced Bone Age
1- Hypothyroidism	1- Hyperthyroidism
2- Hypopituitarism	2- Hyper pituitarism
3- Delayed puberty.	3- Androgen excess (e.g. congenital adrenal hyperplasia)
4- Cushing syndrome	4- Simple obesity.
5- Chronic illness / under nutrition	

Example for bone age estimation by Greulich-Pyle bone age scale



Average bone age 1 year



Average bone age 2 years



Average bone age 3 years

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V. Growth Charts (Curves)

Values

- 1- Assess growth and normal growth variations among children
- 2- Early predictor of malnutrition (flattening of weight curve)
- 3- Monitor success of treatment of malnutrition

Examples

1. Percentile growth curves

Each chart is composed of 7 curves

- 97th percentile → Highest normal.
- 90th percentile → High normal.
- 75th percentile → Above average.
- 50th percentile → Average.
- 25th percentile → Below average.
- 10th percentile → Low normal.
- 3rd percentile → Lowest normal.

Normal child on percentile curves

- Should lie between the 3rd & 97th percentile curves. So, values < 3rd or above 97th are abnormal.
- On serial measurement deviation of the child from his own percentile curve is abnormal.
- Not all the child growth parameters necessarily fall into the same percentile.

2. Growth velocity curves

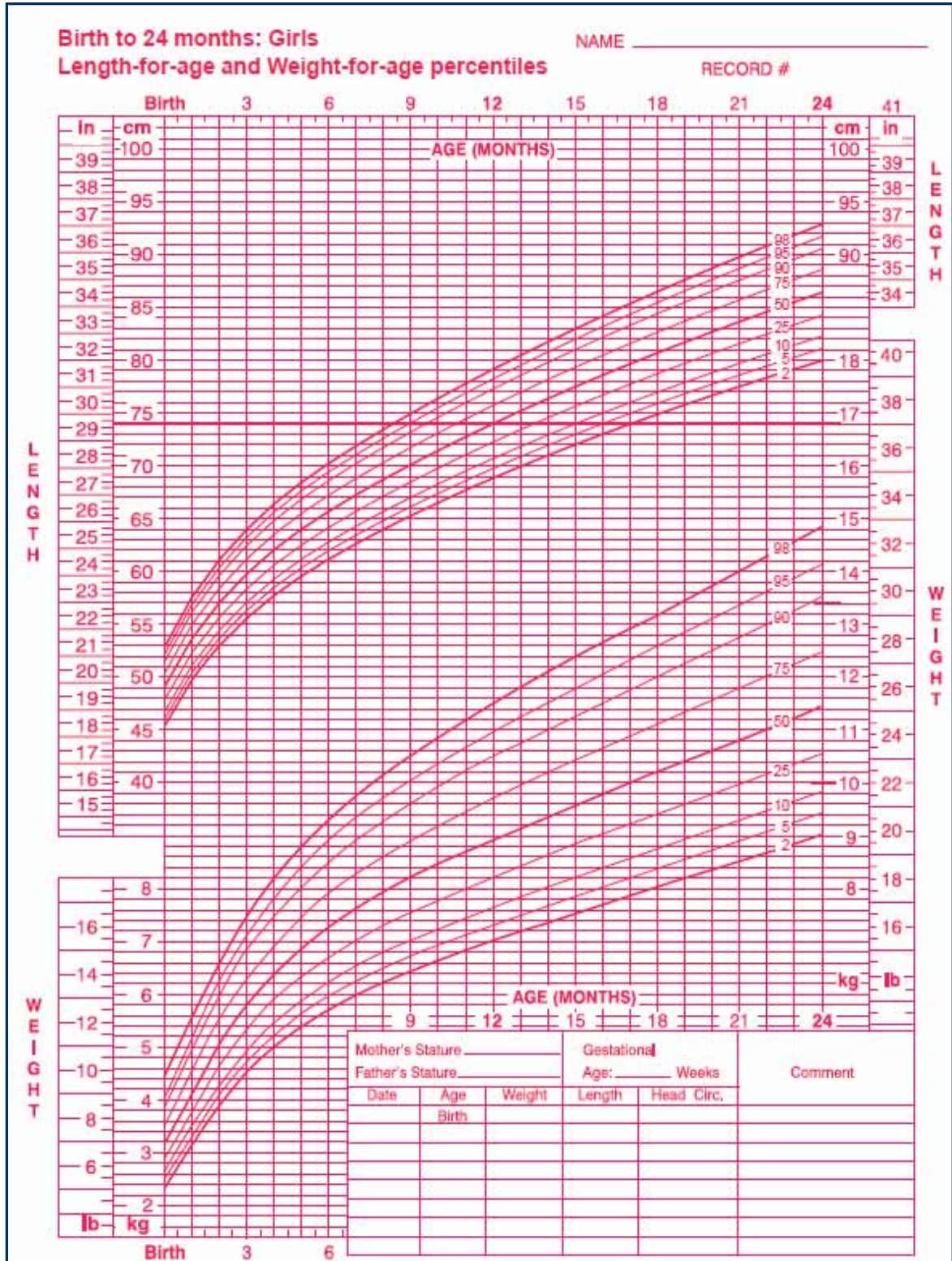
Rate of growth is maximal in infancy and during pubertal spurt

N.B

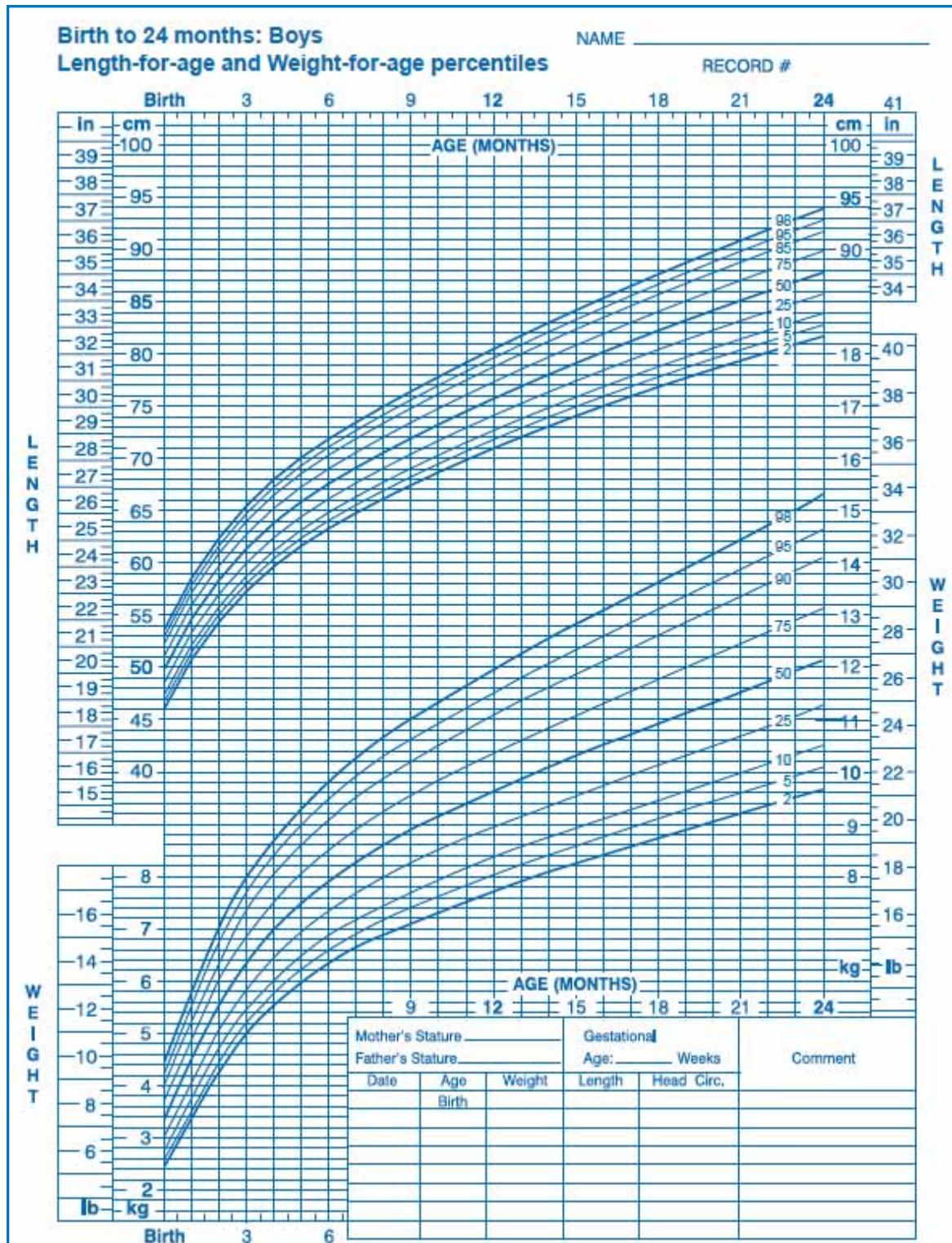
- Weight for height below the 5th percentile remains the single best growth chart indicator of acute under nutrition
- Decreased height for age with normal weight for age indicate nutritional disorder in the past
- Decreased both weight for height with normal height for age indicate both recent and past nutritional disorder
- Specialized charts have been developed for children with :
 - Very low birth weight and prematurity
 - Down
 - Turner
 - Klinefelter syndromes
 - Achondroplasia

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Examples of centile charts



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Assessment Of Development

Motor Milestones : (Locomotor development)

		
Head support ; no head lag	Sit without support	Crawls
3 months	6 months	9 months
		
Stands	Walks	Runs
10 months	12 months	18 months
		
Climbs stairs	Rides a tricycle	Dresses himself
2 years	3 years	





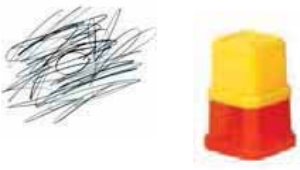


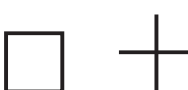

Mental milestones

A. Social development

			
Social smile on social contact	<ul style="list-style-type: none"> • Recognizes mother • Excited at sight of food 	<ul style="list-style-type: none"> • Recognizes father • Stranger awareness 	<ul style="list-style-type: none"> • Finger feeds • Waves bye bye
2 months	4 months	9 months	12 months

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B. Fine motor

 <ul style="list-style-type: none"> • Play with hands in midline • Grasp offered rattle 	 <ul style="list-style-type: none"> • Outreaches objects, mouth it and transfers it 	 <ul style="list-style-type: none"> • Pincer grip
4 months	6 months	9 months
 <ul style="list-style-type: none"> • Casting 	 <ul style="list-style-type: none"> • Tower of two cubes • Scribbles 	 <ul style="list-style-type: none"> • Turn pages in 2-3 pages
12 months	15 months	18 months
 <ul style="list-style-type: none"> • Cut with scissors • Copies a circle 	 <ul style="list-style-type: none"> • Copies a cross & square • Recognize 3 colors 	 <ul style="list-style-type: none"> • Copies a triangle • Draws man with six parts
3 years	4 years	5 years

C. Speech development

- At - 10 months → Says Mama or Dada
 - 1 year → Speaks first real 3 words
 - 19 months → Speaks 2-word sentences (e.g., "Mommy shoe")
 - 2 years → Says 3 word sentences (phrases).
 - 3 years → Says his name & age
 - 5 years → Says clear speech

Criteria of speech delay

- No first words by **15 months**.
- No real words by **18 months**.
- No word combinations by **2 yrs**
- Speech is difficult for others to understand at **3 years**

D. School achievement

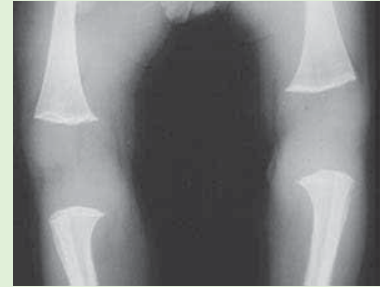
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Self Assessment Clinical Cases

Case 1

A 3-month-old girl, comes in for her checkup with her mother. Her mother complains that her baby is not active, sleeps much and cries little with persistence of the yellow tinge of skin and sclera since the first week of life. You requested a plain radiograph for her knees

- What does the x ray show?
- What is the expected diagnosis?
- What do you expect from examining her fontanel?



Case 2

Bone age will be advanced in short stature caused by which of the following?

- Environmental deprivation syndrome
- Hypopituitarism
- Hypothyroidism
- Congenital adrenal hyperplasia
- Chronic administration of glucocorticoids in high doses

Case 3

An infant can lift his head from a prone position 45° off the examining table, smiles when encouraged, and makes cooing sounds. He cannot maintain a seated position. The most likely age of the infant is

- 1 month
- 3 months
- 6 months
- 9 months
- 12 months

Case 4

A child is brought to your clinic for a routine examine. She can dress with help, can ride a tricycle, knows her own age, and can speak in short sentences. She had difficulty in copying a square. The age of this child is most likely

- 1 year
- 2 years
- 3 years
- 4 years
- 5 years

(Source: Pretest Pediatrics for USMLE)

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Infant feeding

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الدفعة الـ 14

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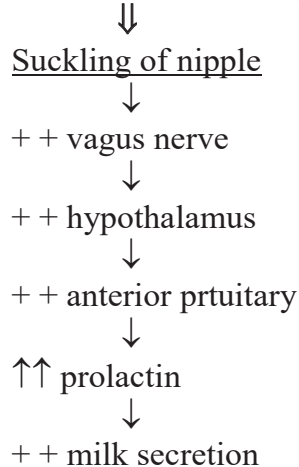
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Breast Feeding

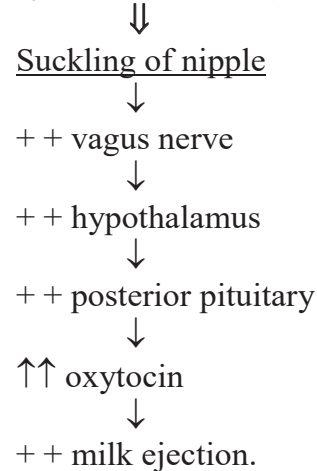
Control of milk production

1. Maternal Reflexes

1. Prolactin (Production) reflex



2. Milk ejection (let down) reflex



2. Infant Reflexes

- Rooting reflex: Infant turns his head to the side where the nipple is felt
- Suckling reflex: Rhythmic movements of the mandible
- Swallowing reflex (Coordinated suckling and swallowing occurs in babies born after 34 completed weeks)

N.B: Maternal anxiety, stress and fatigue inhibits ejection reflex

Breast milk flow is maintained by

1. Mechanical factors: The main stimulus for breast milk flow .It is achieved by:
 - Suckling: the more regular & vigorous suckling, the more the milk flow.
 - Suckling initiate prolactin and milk ejection reflexes
2. Good maternal nutrition with plenty of:
 - Sugary fluids (not evidence based)
 - Vitamins B complex
3. Good maternal psychology (maternal anxiety & stress inhibits ejection reflex)
4. Hormonal balance
5. Rooming in (keeping the baby in mothers room) and skin to skin contact.
6. Demand feeding (feeding according to the infant desire)

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Disadvantages of breast milk

- 1- Breast milk protein Allergy → very rare condition
- 2- Breast milk jaundice may occur due to pregnandiol secreted in breast milk.
- 3- Deficient Content of:
 - * Vitamin K; to avoid bleeding tendency, 1 mg Vit. K is given IM at birth
 - * Vitamin D and Iron:

American Academy of Pediatrics recommends supplementation with:

 - Begin daily oral vitamin D drops (400 IU) at hospital discharge
 - Iron (1-2 mg/kg/d) starting at age 4–6 months until age 1 year
- 4- Some **Drugs** are secreted in breast milk e.g. cytotoxics and antithyroid drugs
- 5- Some viruses are **Excreted** in breast milk e.g. CMV and HIV

Breast Milk Composition

- ✧ Colostrum → milk from birth to the 5th day of life
- ✧ Transient milk → milk from the 5th day to 21st day
- ✧ Mature milk → milk after the 21st day.

	Colostrum	Mature milk
Amount	40-60 ml	1 liter
Reaction	Slightly alkaline	Neutral
Color	Lemon yellow	Whitish
Consistency	Thick	Thin
Caloric value	57 cal/dl	67 cal/dl
Specific gravity	1040 – 1060	1030 – 1035
Protein	7 gm%	1.2 gm%
Fat	3 gm%	4 gm%
Carbohydrates	4 gm%	7 gm %
Colostrum corpuscles (Large endothelial cells from breast acini or fat laden leucocytes)	Normally present	Absent (if exist, it denotes deteriorating breast milk secretion)
Value	1. Nutritive (↑ protein) 2. Protective → ↑↑ Ig A & ↑ PMNLs & monocytes 3. Initiate gastrocolic reflex → mild laxative	See later

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Advantages of Breast Feeding

The AAP and the WHO recommend that infants should be exclusively breastfed or given breast milk for 6 months. The decision to breastfeed should be considered a public health issue and not only a lifestyle choice

I. Advantages to the mother

- 1- Help involution of the birth Canal and reduce risk of post partum hemorrhage.
- 2- Natural method of Contraception.
- 3- Reduce the incidence of Cancer breast.

II. Advantages to the infant

A. Qualitative differences between human and cow's milk

	Human milk	Cow's milk
1. Protein		
a. Dietetic protein		
- Soluble (lactalbumin)	- 60%	- 20%
- Insoluble (casein)	- 40%	- 80%
- Soluble/Insoluble ratio	- 3:2	- 1:4
	Protein is fine and thin and easily digested	Protein is tough & thick And hardly digested
b. Non dietetic protein		
- Lactoferrin level	- High → Static to E.coli → ↑ iron absorption → Immunomodulator	- Traces
- Immunoglobulins	- High (specific to human Pathogens)	- Traces (Specific to animal pathogens)
- Lysozymes level	- High → bactericidal	- Traces.
- Essential amino acids	- High → essential for brain development	- Traces.
2. Fat		
- Fat globules size	- Smaller size → easy digestion	- Larger size → hard digestion
- Diurnal variation	- Present → high concentration at the evening & end of feed	- Absent
- Lipase enzyme level	- High → help digestion	- Lower level
- Essential fatty acids	- Higher (11%) especially Leinoleic and oleic acids.	- Lower level
- Volatile fatty acids.	- Low level → less GIT upsets	- High → frequent GIT upsets → regurgitation & distention

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3. <u>Carbohydrate</u>	<ul style="list-style-type: none"> - β lactose → no fermentation (no gases nor vomiting) - Some is converted to lactic acid: <ul style="list-style-type: none"> → ↑ Calcium absorption. → Bacteriostatic effect 	<ul style="list-style-type: none"> - α lactose → high incidence of fermentation → excess gases, and vomiting.
4. <u>Minerals</u>		
<ul style="list-style-type: none"> - Amount - Calcium/Phosphate ratio - Sodium content - Iron 	<ul style="list-style-type: none"> - Low - 2/1 ; so absorption is better and rickets is less common - Low (less renal solute load) - Low with good absorption sufficient for 1st 4 – 6 months 	<ul style="list-style-type: none"> - High → high risk of hypernatremia - 4/3 so less absorption → high risk of rickets - High - Very low with bad absorption (less bioavailable)
5. <u>Bacterial content</u>	- Sterile	- Liable to contamination

Breast milk contains numerous growth factors e.g.

- Epidermal growth factor: promote repair of intestine
- Transforming growth factor (TGF): Promotes epithelial cell growth
- Nerve growth factor: Promotes neural growth

Breast milk is suggested to protect against: acute diarrhea, otitis media, urinary tract infections, necrotizing enterocolitis, DM, Crohn, Celiac and Cancer

Breast milk for premature is characterized by

1. Protein is higher by **20%** with higher immunoglobulins and lactoferrin.
2. Fat is higher by **50%** with higher content of long chain polyunsaturated fatty acids, which are essential for brain and retinal growth.
3. Vitamins → higher content of vitamins A & E.
4. Carbohydrate → lower lactose content.
5. Contain platelet activating factor acetylcholinesterase & IL-10 which protect against necrotizing enterocolitis (NEC)

- Human milk has concentrations of calcium and phosphorus that are appropriate for full-term infants.
- These amounts are inadequate for the very low birth weight (VLBW) infant. Breast milk should be supplemented with additional calcium, phosphorus, and vitamin D, which can easily be done with a powdered human milk fortifier (Enfamil Human Milk Fortifier, Similac Human Milk Fortifier)

(Nelson textbook of pediatrics)

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B. Anti-infective properties of breast milk

I. Humoral immunity

1. Breast milk contain Antibodies (humoral immunity) against

- Viruses: e.g. Poliomyelitis, mumps, rota virus.
- Enteric bacteria: e.g. E.coli, cholera.

2. Anti staph factor: a polyunsaturated fatty acid.

3. Anti-protozoal: Lipase enzyme kills Entameoba histolytica & Giardia lamblia

4. Antimicrobial enzymes

- Lysozyme
- Lactoperoxidases

5. Bifidus factor

- Nature: Amino sugar
- Role: stimulate growth of lactobacillus bifidus which is a normal bacteria flora in the intestine → interference with pathogenic bacteria as E. coli & vibrio cholera.

6. Binding proteins

- Nature
 - Folic acid binding protein.
 - B₁₂ binding protein.
 - Lactoferrin; Iron binding protein
- Role: Folic acid, B₁₂, and iron are essential for growth of pathogenic bacteria ; binding proteins deprive pathogenic bacteria from these growth factors with subsequent bacteriostasis.

II. Cellular immunity

a. Polymorphnuclear leucocytes and macrophages which can

- Secrete lysozymes, complement, and lactoferrin
- Phagocytose and kill bacteria and fungi

b. Lymphocytes:

- T lymphocytes provide cell mediated immunity
- B lymphocytes secrete antibodies ; mainly IgA

III. Others

- Low buffering effect: neutral or slightly alkaline milk pH preserves gastric acidity which acts as a barrier against infection
- Low incidence of necrotizing enterocolitis (NEC)
- Oligosaccharides and κ-casein: Prevent bacterial attachment
- Nucleotides: Enhance antibody responses and bacterial flora

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Efficiency (Adequacy) of breast feeding

Evidence of adequate feeding

1. Adequate weight gain on serial assessments (the most important clue)
2. Satisfaction after feeding; the baby sleeps 2-3 hours after feedings
3. Normal bowel habit: no diarrhea or constipation
4. Normal urine flow

5. Test feed

- Weigh the infant before & after feeding with unchanged clothes 6 times a day
- Calculate amount of the feed for 3 days and then take the average

Abnormalities of breast feeding

	Under feeding	Over feeding
Manifestations	<ul style="list-style-type: none"> * Exaggerated initial weight loss Followed by poor weight gain * None satisfaction post feed <ul style="list-style-type: none"> - Stay suckling for longer - Stay alert after feeds - Excessive crying - Sucking fingers (hungry!!) * Delayed stooling * Oliguria * Hypernatremic dehydration may occur 	<ul style="list-style-type: none"> * Excessive weight gain * Excessive crying & irritability due to colic and distension * Repeated vomiting * Bulky stool (may be diarrhea) * May be polyuria * May be sore buttocks.
Management	<ul style="list-style-type: none"> * Direct observation of breast-feeding can help identify improper technique * Examine both infant and Mum for a treatable cause * Supplemental formula 	<ul style="list-style-type: none"> - Space feeds apart - No suckling > 20 min / feed. - Remove excess breast milk by pump <u>post</u> feeding

Intervals between feeds (Ideally 3 hours intervals = gastric emptying time)

2 hourly feeding for	4 hourly feeding for
<ul style="list-style-type: none"> • First 2 weeks of life. • Weak sucker • Scanty milk flow. 	<ul style="list-style-type: none"> • After the 4th month. • Overweight and strong suckers. • Liberal milk flow.

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Contraindications of breast feeding

I. Maternal causes

Temporary	Permanent
1. Bilateral nipple fissuring. 2. Bilateral acute mastitis & abscess 3. Infectious diseases e.g typhoid 4. Mothers on temporary medicines that is known be secreted in milk and may harm the baby	1. Malignancy 2. Active maternal CMV Infection 3. Maternal use of certain radioactive isotopes, cancer chemotherapy agents, and a small number of other medications (<i>See The Lactmed Database online for further details</i>)

Active, untreated maternal tuberculosis

A. **Current recommendation** (American Academy of Pediatrics, 2014):

- Baby is separated from mother until completion of 2 wk of maternal therapy
- During this period milk is expressed for the baby to be fed via bottle

B. Other opinion: Mums can lactate with the following precautions:

- Mum receives anti T.B drugs and uses mask during feeding
- The baby receives prophylactic isoniazid 10 mg/kg/d (*Window prophylaxis*)
 - Continued until the mother has been shown to be sputum culture negative for ≥ 3 mo
 - At that time perform Mantoux skin test
 - a. Positive test: INH is continued for a total duration of 9-12 mo
 - b. Negative test: stop INH & vaccinate the infant with INH resistant BCG
- Separation is considered if the mother:
 - Suspected to have drug resistant TB
 - Acutely ill
 - Non adherent to treatment

Infant to HIV mothers

- In developed countries :breast feeding is contraindicated where safe nutritional alternative is readily available
- In other regions: risk of viral transmission if feeding allowed must be weighed against risk of developing malnutrition if breast feeding withheld

Infant to HBsAg positive mothers

Breast feeding is allowed provided the baby got both the HBV vaccine & Ig

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I. Infant causes

1. Milk protein allergy: Extremely rare.

C/P - Colic ,vomiting, diarrhea
- May be bloody stool or occult blood in stool.

Treatment - Hypo allergenic formula

2. Lactose intolerance

Due to - Lactase deficiency ; primary or secondary to gastroenteritis

C/P - Accumulated lactose in intestine leads to:

- Fermentation → abdominal distension ,colic &vomiting
- Osmotic diarrhea → reducing substance in stool.
- Change to lactic acid → acidic motions → perianal soreness
→ stool pH < 5

Treatment - Lactose free formula

3. Galactosemia: Autosomal recessive disorder

Normally: Lactose $\xrightarrow[\text{enzyme}]{\text{Lactase}}$ Glucose + Galactose -1-Phosphate (Gal-1-P)

Gal-1-P $\xrightarrow[\text{Uridyle transferase}]{\text{Galactose 1 phosphate}}$ Glucose.

In galactosemia : absent Gal-1-P uridyl transferase→ accumulated Gal-1-P leads to:

- Cataract (absent red reflex in newborn)
- Chronic active hepatitis, hepatomegaly
- Mental retardation

Treatment: lactose/galactose-free formula



4. Phenylketonuria: Autosomal recessive disorder

Normally: Phenylalanine $\xrightarrow[\text{hydroxylase}]{\text{Phenylalanine}}$ Tyrosine & Tryptophan

In phenylketonuria : Defective phenylalanine hydroxylase enzyme leads to:

- Fair skin , hair and blue eyes
- Cerebral palsy and seizures
- Mental retardation.

Diagnosis

- Positive screening test of Guthrie
- Phenylalanine > 1200 mol/L + Normal / low tyrosine

Treatment: Phenylalanine low formula (contain tyrosine)



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Problems with breast feeding

Nipple Pain

- Common complaint in the immediate postpartum period
- Due to poor infant positioning and improper latch and or nipple candidiasis

Treatment

- Treat both mother and baby if candidiasis is found.
- If accompanied by engorgement, express milk manually until healing has occurred (*Breast milk can be refrigerated and used within 48 hours. Frozen milk can be used for up to 6 months-thawing should be by warm water but never in microwave!*)

Engorgement

- Incomplete removal of milk due to poor breast-feeding technique or other reasons such as infant illness
- The breasts are firm, overfilled, and painful

Treatment

- Frequent breast-feeding
- Manual milk expression before breast-feeding may be required.

Mastitis

- Presentation
 - After the 2nd post-delivery week
 - Usually unilateral localized warmth, tenderness, edema, and erythema.
 - Sudden onset of breast pain, myalgia, and fever.
- Organisms implicated
 - Staphylococcus aureus, Escherichia coli, group A streptococcus, Haemophilus influenzae, Klebsiella pneumoniae, and Bacteroides spp.

Treatment

- Oral antibiotics and analgesics
- Promote breast-feeding or emptying of the affected breast
- Breast abscess: Intravenous antibiotics as well as incision and drainage, along with temporary cessation of feeding from that breast.

Jaundice

a. Breast-feeding jaundice

- Largely related to insufficient fluid intake
- Commonly associated with exaggerated physiologic weight loss $\geq 12\%$
- It may also be associated with dehydration and hypernatremia

b. Breast milk jaundice (See neonatology)

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Artificial Feeding

Defined as supplying any milk other than breast milk

Indications

1. Substitutive feeding (all breast feeds are replaced by bottle feeds)

- Absent mother
- Contraindications to breast feeding (maternal or infant causes) .

2. Mixed feeding

a. Complementary feeding (Breast feeds are completed by bottle feeds)

- Indicated when breast milk is not enough (scanty breast milk secretion)
- Precautions:
 - Breast milk should be given first and completely emptied.
 - The used milk should be humanized formulas.
 - Formula should not be sweetened
 - Bottles holes should not be large

b. Supplementary feeding (some breast feeds are replaced by bottle feeds) for:.

- Working mother.
- Twin delivery (breast and bottle given to each baby alternatively)

Disadvantages:

- Liable to Contamination.
- Costly
- Lack advantages of breast milk

1. Fresh fluid animal milks

Types:

- * Cow's milk → most commonly used worldwide.
- * Buffalo's milk → most commonly in Egypt.
- * Goat's milk
- * Ass milk → near in composition to human milk.

Specific disadvantages

A. Drawbacks of Goat's milk:

- Low folic acid → ↑ incidence of megaloblastic anaemia
- High risk of brucellosis.

B. Drawbacks of cow milks:- (*See comparison between breast & cow milk*)

1. High incidence of diarrhea, respiratory infections & allergies
2. High risk of iron deficiency anemia due to:
 - Low iron content with poor absorption
 - Low lactoferrin content.
 - Occult blood loss due to heat labile protein.

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2. Dried powdered milk formula

* Dried powdered milk formula are based on cow milk in most cases

Advantages

- 1- Can be modified, so Fits for different infant needs.
- 2- Fortified with vitamins , minerals, and trace elements

1. Humanized formulas

Modifications: Modified to be very similar to breast milk :

- Protein is modified to form a fine curd
- Carbohydrate content is increased.
- Fat is refined with increased poly unsaturated fatty acids
- Vitamins (especially vitamin D & C) are added
- Calcium: phosphate content reduced and ratio adjusted
- Trace minerals are added particularly Iron , copper & zinc

Indications : - Healthy infants when breast milk is scanty or unavailable
 - Large prematures (2-2.5 kg)
 - Milder degrees of malnutrition

Examples : - Novalac , Bebelac, Nan, Biomil, Aptamil
 ⇒ 1 spoonful (4gm) for each 30 ml water.
 - Similac , S-26
 ⇒ 1spoonful (8gm) for each 60 ml water.

N.B (May be numbered as 1 for the 1st 6 months of life, 2 for the next 6 months of life, and may be 3 for after 1 year of life)



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2. Lactose free formula

Modification : - Lactose is replaced by other sugar (sucrose or glucose)

Indications : - Lactose intolerance.
- Galactosemia

Examples : - Enfamil LactoFree, S26-LF, Isomil



3. Hypoallergenic formula

A. Casein hydrolysate based formula

1. Partially hydrolyzed

Containing oligopeptides with a molecular weight of <5000 d
Or

2. Extensively hydrolyzed

Containing peptides with a molecular weight <3000 d.

Indications

- Prevent or delay atopic dermatitis
- Infants intolerant to cow's milk or soy proteins
- These formulas are lactose free and can include medium-chain triglycerides, making them useful in infants with malabsorption

Examples

- Aptamil Pepti 1 and 2
- Pepti junior
- Pregestimil



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B. Amino Acid Formulas

Amino acid formulas are peptide-free formulas that contain mixtures of essential and nonessential amino acids.

Indications

- Infants with dairy protein allergy who failed to thrive on extensively hydrolyzed protein formulas
- For severe Cows' milk allergy, and multiple food protein intolerance

Examples

- Neocate LCP
- Nutramigen AA (Gluten & Lactose-free)
- EleCare (Similac)



N.B (Soy protein based formula e.g. Isomil is not fit for cow milk allergy due to cross allergy but can be used as a lactose free formula)

4. Preterm infant formula

Modification : - More protein , medium chain triglycerides, vitamins and calories(80 calories /100 ml)
- Lower lactose.

Examples : - Enfamil EnfaCare, Enfalac premature, Similac expert care



5. Pre-thickened formula

Indications : - Regurgitations and Gastro esophageal reflux disease

Modification - Contain pregelatinised rice starch or cooked corn starch

Precaution : - Not to be used for a period of > 6 months
- Not to be used in conjunction with antacid products

Example : - Enfamil AR



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6. Amino Acid-Modified (Metabolic) Formulas

a. Phenylalanine low formula

Indications : - Phenylketonuria

Example : - Lofenalac



b. Branched chain amino acid free formula

Nutrition support of children with maple syrup urine disease

Supplemented with L-carnitine and taurine

Example: Ketonex



c. Methionine-free formula

Nutrition support of children with homocystinuria

Example: Hominex



7. Formulas for specific diseases

a. Nutrition support for babies with renal failure

Modifications:

- High calorie with low fluid volume
- Low salt , low protein
- Low potassium ,and phosphorus

Examples:

- Renastart
- Suplena
- Nepro



b. Nutrition support for children with acute or chronic liver failure

- Generaid
- Heparon Junior



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Program of Artificial Feeding

1. Decide type of milk

* According to:

1. Whether the baby is healthy (R/ humanized formula) or not
2. Financial conditions of the family

* Use either:

- Dried powdered milk
- Fresh fluid animal milk(not preferred in the 1st year of life).

2. Determine the amount of milk needed by

a- Age method

- Valid only for healthy full term .
- Amount of milk (ml/feed) = $\text{Age in days} \times 10$
 $\text{Age in weeks} \times 10 + 70$
 $\text{Age in months} \times 10 + 100$

b- Caloric(weight) method

- this method is valid for both the healthy and diseased babies
- More accurate than age method
- Calculation:
 - ⊕ Normal healthy infant needs 110 cal/kg/d.
 - ⊕ Milk contain 67 cal/per 100 ml.
 - ⊕ So total daily need of milk = $100/67 \times (110 \times \text{body weight in kg})$.
 - ⊕ This total amount is divided into feeds.

3. Formula (concentration of milk)

i- Formula of dried powdered milks:

- ⊕ One measure of 4 gm diluted by 30 mL boiled water e.g. Bebelac
- ⊕ One measure of 8 gm diluted by 60 mL boiled water e.g. Similac

ii- Formula of fresh fluid animal milk (not recommended !!!)

4. Number of feeds per day: According to age; roughly

- Between 0-4 months → every 3 hours
- Between 5- 8 months → every 4 hours
- Between 9-12 months → every 5 hours

5. Determine method of feeding: According to age & condition: Bottle, tube, or dropper

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Weaning

Introduction of semisolid and solid foods besides breast milk or formula

Values

- Compensate for increasing infant needs that can not be fulfilled by breast milk alone.
- Train the gastrointestinal tract and train the baby to use cup and spoon.
- Supply vitamins and minerals e.g. A , D , C , iron , zinc and calcium

When to initiate?

- * Begin weaning at **6 months** of age: Why?
 - Maturation of digestive enzymes occur
 - Decline of minerals and vitamin stores
 - Caloric value of breast milk becomes inadequate.
- * Never try before 4 months due to:
 - Digestive enzymes of the infant have not developed yet
 - Breast milk is sufficient in the 1st 4 months of life
 - Risk of developing allergies

When to complete?

- * At 1.5 to 2 years

Guidelines of weaning? (By American Academy of Pediatrics; Nelson 2016)

- Serve foods immediate after preparation
- Stepwise weaning
 - Introduce 1 food at a time
 - Small amount of one food is started and increased gradually
 - Do not introduce other new foods for 3-5 days to observe for tolerance
 - Feed slowly, do not force; many trials may be needed as spitting can occur.
- During illness give breast feeding and increase food intake after the illness.
- At the proper age, encourage a cup rather than a bottle
- Energy density should exceed that of breast milk
- Iron-containing foods (meat, iron-supplemented cereals) are required
- Zinc intake should be encouraged with foods such as meat, dairy products, wheat, and rice
- Phytate intake should be low to enhance mineral absorption
- Breast milk: exclusive in the first **6 months** and should continue to **12 mo**
- Fluids other than breast milk, formula, and water should be discouraged

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How to start? Suggested plan

Age	Suggested food
6 mo.	Cereals, cornflower puddings (Cerelac) ,biscuits
7 mo.	Rice , Rice pudding , cheese and mashed fruits
8 mo.	Vegetable soups in water and yogurt, egg yolk
9 mo.	Beans and vegetable soup in meat
10 mo.	Mashed liver and meat
11 mo.	Poultry and rabbits
12 mo.	Mashed red meat , fish
In the 2 nd year	Other family foods including fresh animal milks

What food to avoid?

- Canned foods
- Salt and spices
- Use of whole Cow milk below 1 year
- Sugar : no sugar sweetened beverages
- Chocking foods(e.g. nuts, grapes, raw carrots) in the first 3-4 years
- Allergenic foods e.g. Egg white
- Fruit juices during the first 6 mo of life and limited amounts of juices thereafter (120-180 ml /day for ages 1-6 yr)

Problems with weaning

- 1- Allergies → may follow some new foods e.g eggs,
- 2- PCM → sudden weaning on starchy foods → Kwashiorkor (KWO).
- 3- Colic is common especially with:
 - Excess sugary fluids
 - Early aggressive weaning
- 4- Diarrheal disorders → gastroenteritis due to contaminated foods.
- 5- Dental caries: associated with excess carbohydrates and bottle feeding.
- 6- Delayed weaning may predispose to:
 - Marasmus
 - Iron deficiency anemia.
 - Rickets.
- 7- Some Diseases may manifest during period of weaning: e.g.
 - Favism
 - Celiac disease

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Self Assessment Clinical Cases

Case 1

You are reviewing this 8 months old, breast fed baby boy who had gastroenteritis for the previous 2 weeks, now he is irritable, has distended abdomen, still having mild watery diarrhea and some peri anal soreness

- a. What is your diagnosis?
- b. How can you confirm it?
- c. What is your decision?

Case 2

Lactating mother with an acute medical condition cannot feed her full term normal male infant 2 mo age & 4 kg weight for about 3 days. His grandmother will take care of him.

- a. What is the type of artificial milk appropriate for him?
- b. What is the number of feeds/ 24 hr?
- c. How much is the amount of milk required /feed?
- d. How can she prepare the formula (concentration of milk given)?

Case 3

A 10 months old, breast fed boy who was switched to cow milk at 9 months as his mother has to return work, the mother complains that her baby becomes irritable, with more frequent vigorous crying episodes, vomiting and distension with occasional bloody stool; his weight declined from 8.7 kg to 6.5 kg

- a. What is the provisional diagnosis?
- b. What is the laboratory test required?
- c. What is the preferred formula for this boy?

Case 4

A list of artificial milks

- A. Humanized formula
- B. Lactose free milk
- C. Premature formula
- D. Phenylalanin low formula
- E. Predigested formula
- F. Hydrolyzed formula

From list above select the milk suitable for the following cases:

1. Diarrhea that continues for 2 weeks following an attack of Rota virus gastro enteritis
2. Diarrhea that continues for more than 2 months with failure to thrive
3. A 1.8 kg newborn that developed neonatal seizures who has fair skin and hair and whose urine shows abnormal urine aminogram
4. A 1.8 kg newborn who developed neonatal seizures and abnormal liver function and abnormal red reflex
5. A 1.8 newborn that just recovered from RDs

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الدفعة الـ 14



Nutritional disorders

Protein Calorie Malnutrition (PCM)

[Protein Energy Malnutrition ;PEM]

Classifications of PCM

1. Wellcome classification: Based on weight for age & presence of edema.

Ratio of current weight to expected weight for age	Symmetrical Oedema	Diagnosis
> 80%	++	Nutritional edema or KWO
60-80%	--	Simple underweight
60-80%	++	Kwashiorkor (KWO)
< 60%	--	Marasmus
< 60%	++	Marasmic KWO

2. Waterlow Criteria

A. Changes in weight may be an indicator of acute malnutrition.

$$\frac{\text{Actual wt (kg)} \times 100}{\text{Expected wt for ht at 50}^{\text{th}} \text{ centile}}$$

Expected wt for ht at 50th centile

- Grade 0 : $\geq 90\%$ → Normal
- Grade I : 80%–89% → Mild
- Grade II : 70%–79% → Moderate
- Grade III : $< 70\%$ → Severe

B. Changes in height may be an indicator of chronic malnutrition.

$$\frac{\text{Actual ht (cm)} \times 100}{\text{Expected ht for age at 50}^{\text{th}} \text{ centile}}$$

Expected ht for age at 50th centile

- Grade 0 : $\geq 95\%$ → Normal
- Grade I : 90%–94% → Mild
- Grade II : 85%–89% → Moderate
- Grade III : $< 85\%$ → Severe

3. WHO criteria

- Wasting: Low weight for height(WFH) below the median
- Stunting : Low height for age (HFA) below the median

4. Kanawati criteria

- Uses MUAC divided by occipitofrontal head circumference(see before)
- Malnutrition degree: Mild < 0.31 , moderate < 0.28 , severe < 0.25

(Nelson Textbook of Pediatrics and Texas Children's Hospital Handbook of Pediatrics, 2016)

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Kwashiorkor (KWO)

(Edematous PCM, Red Baby)

Definition

- Acute protein deficiency with normal or even high caloric intake
- “The sickness the baby gets when the new baby comes” in Ghana language

Incidence

- More frequent in babies whose mums are poor , and ignorant
- KWO usually affects infant ages between 6 months to 2 years

Causes

Main factor

- Sudden faulty weaning on starchy, carbohydrate, protein deficient diet.
- Maternal deprivation: the 1st baby is neglected (affected) when a 2nd is born

Contributing factors :infections e.g.

- Pertussis → recurrent vomiting.
- Chronic diarrhea and parasitism → protein loss in stool.
- Measles → complicating enterocolitis.

Clinical Picture

Constant features

1. Edema



- Starts in the dorsa of feet & hands then the upper and lower limbs
- Edema is bilateral, pitting & painless
- With shiny overlying skin
- Ascites and pleural effusion are usually absent



- Facial edema produce prominent pale cheeks → Doll facies
- Periorbital edema

Etiology of edema

- Hypoalbuminemia → reduced plasma osmotic pressure
- Decreased anti-oxidants → *free radical* damage → ↑ capillary permeability
- Other proposed causes: ↓ Na/K-ATPase activity & aflatoxin poisoning
- Increased Aldosterone and ADH → salt and water retention

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Grading of edema

- Grade 1: mild edema on both feet or ankles
- Grade 2: moderate edema on both feet, lower legs, hands, or lower arms
- Grade 3: severe generalized edema affecting limbs & face

2. Mentality changes

- Patient looks dull , apathetic, miserable, disinterested in surroundings with marked anorexia
- Global developmental delay in severe malnutrition

Due to

- * ↓ Aromatic amino acids → ↓ Neurotransmitters
- * Maternal deprivation.



3. Growth retardation

- Failure to gain weight followed by weight loss
- Length is much less affected as KWO is acute disease.
- Weight loss may be masked by edema and preserved subcutaneous fat

4. Muscle wasting

- Muscles are thin, atrophic & weak
- Decreased mid upper arm circumference < 12 cm
- Head circumference / chest circumference ratio > 1

Variable features

1. Hair changes

- Hair is lusterless , brittle, sparse, easily pickable
- Progressive lightening of hair; black → brown → reddish → yellow → gray
- Flag sign:
 - Alternating bands of light color & normal color
 - In long haired with relapses of malnutrition
- Due to tyrosine and copper deficiency (essential for melanin synthesis)



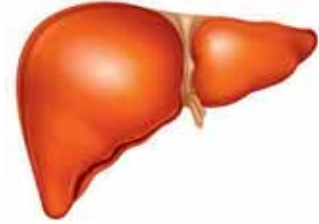
2. Skin changes

- Starts as dry scaling skin → erythema → hyperpigmentation & desquamation (Crazy paving or Flaky paint dermatosis)
- Skin infection is common
- Possible causes:
 - Vitamin A deficiency
 - Essential fatty acids deficiency
 - Zinc deficiency



3. Hepatomegaly

- Caused by fatty infiltration due to decreased lipotropic factors
- No hepatocyte damage (No cirrhosis)
- Hepatomegaly is reversible with treatment.
- Size may increase at the start of treatment if high caloric diet is used due to accumulation of glycogen before disposing fat (nutritional recovery syndrome)



4. GIT manifestations

- Diarrhea due to gastroenteritis and /or Malabsorption
- Abdominal distension may be due to malabsorption or hypokalemia

5. Anemia: May be due to:

- Iron deficiency → hypochromic microcytic anemia
- Protein deficiency → normochromic normocytic anemia
- Folic acid and/or B₁₂ deficiency → megaloblastic anemia

6. Vitamin deficiency

- Vitamin A deficiency (very common) manifested by:
 - Eyes : - Xerosis, Bitot spots
 - Keratomalacia
 - Corneal ulcers and eventual scarring
 - Mouth : stomatitis.
- Vitamin C → spongy bleeding gums
- Vitamin B₂ deficiency : cheilosis, angular stomatitis.
- Vitamin D deficiency : it is usually not manifest due to arrested growth
- Vitamin K deficiency → bleeding tendency.



Complications(DIE B H4)

1- Dehydration: Due to gastro enteritis & anorexia.

2- Intercurrent infections:e.g.

- Gastro enteritis
- TB & bronchopneumona
- Oral moniliasis
- Noma : It is chronic necrotizing ulceration of the gingiva and the cheek
 - May be incited by *fusobacterium necrophorum* & *prevotella* co infection
 - Manifestations: fever, malodorous breath, anemia, leukocytosis



3- Electrolyte disturbances:

- Hyponatremia
- Hypokalemia
- Hypocalcemia & hypomagnesemia ⇒ may be tetany

4- Blindness: due to keratomalacia secondary to severe vitamin A deficiency

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5- Hypothermia**6- Hypoglycemia:** Commonly associated with sepsis**7- Heart failure** due to:

- Severe anemia.
- Volume overload.
- Weak myocardium \Rightarrow dilated cardiomyopathy.

8- Hemorrhage due to:

- Vitamin K deficiency.
- Disseminated intravascular coagulation (DIC)

Investigations**1. To support the diagnosis**

- Plasma proteins:
 - Decreased total plasma proteins < 4.5 gm /dl(normal 6-8 gm/dl).
 - Decreased albumin < 2.5 gm / dl (normal 3.5 – 5 gm/dl).
- Non essential / essential amino acids > 3 (normally ≤ 2 ,between 2-3 in subclinical cases)

2. To detect complications

- Monitor blood glucose closely
- CBC for anemia and leukocytosis in infection
- Sepsis workup e.g. CBC with differential, CRP, urinalysis, stool analysis, blood culture, chest x ray and tests for tuberculosis
- Serum electrolytes/minerals: Na, K, Ca, Mg.

Incomplete KWO (Pre KWO)

The patient shows all constant features of KWO except oedema & all variable features except skin changes

Phenomena which may occur during KWO treatment

1. Hypokalemia: Hypokalemia (already present) is aggravated by glucose infusion

2. Circulatory overload:

With infusion of large doses of blood or plasma $\rightarrow \uparrow$ plasma osmotic pressure \rightarrow shift of fluid from interstitial compartment to intravascular compartment \rightarrow volume overload & heart failure.

3. Initial weight loss: May occur due to absorption of edema fluid.

4. Nutritional recovery syndrome may rarely occur due to either:

- A. Excess caloric intake \rightarrow excess glycogen deposition in the liver before disposing excess fat \rightarrow hepatomegaly may increase at the start of treatment
- B. Excess protein intake > 6 gm/kg/d \rightarrow liver is exhausted by protein metabolism \Rightarrow Excess ammonia load on the liver leads to:
 1. Hepatic encephalopathy with lethargy, convulsions & coma.
 2. Hepatocyte necrosis \rightarrow liver cell failure with hepatomegaly, jaundice, ascites and even liver cirrhosis later on.

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Marasmus

(Failure to thrive or non oedematous PCM with severe wasting)

Definition: Chronic under nutrition with deficiency of both proteins & calories.

Causes

I. Primary (Dietetic)

- Target age: 6 months – 2 years
- Usually in low socioeconomic classes where the mothers are ignorant
- Inadequate food intake due to

A. Low quantity

- Scanty breast milk in breast fed infants
- Scanty or infrequent feeds in artificially fed
- Low caloric diet in older infant

B. Poor quality

- Prolonged breast feeding without supplementation
- Diluted formula in artificially fed
- Reliance on fluids

C. Feeding difficulties: e.g. with bilateral cleft lip and /or palate

II. Secondary (Non dietetic)

1. Preterms and twins: are more prone to marasmus due to:

- High rate of growth in face of weak suckling power and limited capacity for digestion and absorption
- Limited fat stores

2. Chronic infections

- Examples: Tuberculosis, empyema, chronic pyelonephritis, etc...
- Mechanism : Anorexia & hypercatabolic state

3. Malabsorption states/Metabolic diseases

- Recurrent gastro enteritis / Chronic diarrhea
- Malabsorption syndrome due to e.g., Cystic fibrosis, celiac disease.
- Inborn errors of metabolism e.g. Galactosemia ,organic acidemias

4. Pediatric malignancies: via anorexia, hypercatabolism & chemotherapy

5. Congenital anomalies

- Neurologic: e.g. cerebral palsy, mental retardation.
- Congenital heart diseases
- Gastrointestinal e.g.
 - Gastroesophageal reflux disease.
 - Congenital pyloric stenosis.
- Renal anomalies (due to associated UTI & acidosis).

6. Maternal neglect (child abuse; non organic failure to thrive)

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Pathophysiology of Marasmus

- In infants the daily caloric intake is consumed as follows:
 - Basal metabolic rate (BMR) 50 % \Rightarrow unavoidable
 - Physical activity 25 %
 - Growth 12 %
 - Losses and others 13 % \Rightarrow unavoidable.
- When there is caloric deficiency the first compensatory mechanism will be decrease physical activity and arrested growth. With advanced caloric deficiency the body utilizes his own tissues; firstly fat then proteins to maintain BMR which results in marasmus.

Clinical picture

I. Symptoms: (5C)

- Failure to gain weight followed by progressive weight loss(Cachexia)
- Baby is usually hungry: irritable, Crying, sucking fingers with little sleep.
- Constipation due to reduced food intake but may be diarrhea due to starvation (greenish, scanty, offensive with mucus & debris) , gastroenteritis ,malabsorption or maldigestion
- May be features suggesting the Cause
- May be features of Complications e.g. gastro enteritis, pneumonia.

II. Signs

A. Protein deficiency manifestation

1. **Body weight** is less 60% of the normal weight for age without oedema.
 - Loss of 40% of pre illness body weight \rightarrow 1st degree marasmus
 - Loss of 40-50% of pre illness body weight \rightarrow 2nd degree marasmus
 - Loss of > 50% of pre illness body weight \rightarrow 3rd degree marasmus

2. Muscle wasting

- Muscle is sacrificed to keep near normal plasma proteins.
- Muscle wasting is more severe in marasmus than in KWO giving rise to stick like appearance of limbs
- Muscle wasting is detected by decreased MUAC and chest circumference.



B. Caloric deficiency manifestation

1. Loss of subcutaneous fat from

- Abdominal wall (1st degree marasmus)
- Buttocks & limbs (2nd degree marasmus)



- Cheeks (senile face) (3rd degree marasmus)

The buccal pad of fat is the last to be lost as it is unsaturated fat essential for suckling

Outcome

- Skin becomes thin, loose, wrinkled, thrown into folds especially on the medial aspect of the thighs.
- Decreased triceps skin fold thickness
- Prominent normal costochondral junctions in marasmus due to loss of subcutaneous fat are called false rosaries.

2. Hypothermia due to

- Loss of subcutaneous fat → excess heat loss.
- Hypoglycemia → decreased basal metabolic rate.
- Septic shock.

C. Vitamin deficiency, anemia, hair & skin changes may occur as in KWO

D. Signs of an underlying cause in secondary marasmus

Complications

As in kwashiorkor plus (MOAP)

- 1- Muscle fibrosis in advanced cases
- 2- Oedema may occur with development of marasmic kwashiorkor
- 3- Atrophic ulcers over bony prominences
- 4- Purpura due to DIC due to dehydration, toxemia, acidosis



Investigations

1. Biochemical changes in marasmus

- Blood : - Hypoglycemia (due to reduced glycogen stores in the liver).
 - Plasma proteins slightly reduced
- Urine: - Ketonuria (fat hypercatabolism).
 - Increased creatinine (muscles hypercatabolism)

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2. For a cause in the secondary marasmus

- 1- Stool analysis for parasites, stool cultures and *malabsorption workup*
- 2- Urine analysis and culture
- 3- Abdominal sonography.
- 4- Organ function tests (renal & liver functions tests)
- 5- Others :e.g.
 - Chest x-ray
 - Tuberculin test: is commonly negative due to 2^{ry} immunodeficiency
 - Echocardiography for suspected congenital heart diseases.
 - Barium study , endoscopy ± biopsy for suspected GIT diseases

3. For complications ⇒ as in KWO

Death May occurs in severe complications especially due to:

- Hypoglycemia
- Shock (septicemia or dehydration) → disseminated intravascular coagulopathy
- Heart failure

Marasmic KWO: is manifested by:

- Weight < 60% of expected for age with nutritional oedema(*wasting & edema*)
- MUAC < 11 cm with edema
- It occurs mainly in marasmic child fed on carbohydrate diet only without adequate protein → appearance of oedema → marasmic KWO
- Other features of marasmus : loss of subcutaneous fat and marked muscle wasting are present
- Other features of kwashiorkor: mentality changes , dermatosis and hair changes are present



Failure to thrive: this term is considered if

- Child's weight is below the 5th percentile, or
- Child's weight drops down more than 2 major percentile lines in short time, or
- Child's weight for height is less than the 5th percentile.
- ♦ Etiology & management: Same as marasmus.

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Management of PCM

A. Prevention

- Providing micronutrient interventions such as vitamin A and iron supplements for pregnant and lactating women and young children
- Encourage exclusive breast feeding
- Proper weaning .
- Regular check of growth by growth curves to pick early malnutrition which appear as flattening of weight curve
- Deworming in endemic areas & oral rehydration in high-diarrhea regions
- Fortifying commonly eaten foods with micronutrients (such as salt fortified with iodine) and foods like wheat, oil, and sugar with iron, vitamin A, and zinc

B. Curative

I. Inpatient or outpatient care?

- Outpatient care for clinically well, uncomplicated and with good appetite
- Inpatient care for complicated cases, cases with severe edema and marasmus kwashiorkor patients

II. Stabilization phase (In the 1st 1- 7 days) for:

Hypoglycemia

- Glucose 10% oral, or intra venous
- Frequent feeding ; 2 hourly day & night.

Hypothermia

- Proper wrapping/ Warmers
- Treat hypoglycemia & serious systemic infections

Dehydration:

- Preferably oral rehydration solution (ReSoMal)
- Continue breast feeding
- Intra venous fluids for severe dehydration.

Hypoglycemia, hypothermia and dehydration have priority for treatment in the first 1-2 days of management

Electrolytes and minerals correction

- Monitor and correct levels of phosphate, potassium, calcium and magnesium especially with start of feeding (see refeeding syndrome)

Infections

- Appropriate antibiotics
- Specific e.g. Anti tuberculous for T.B.

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Heart failure

- Packed RBCs for anemic heart failure
- Diuretics, vasodilators and cautious use of digitalis

Blood transfusion

- Fresh whole blood transfusion for severe anemia:
20 ml/kg for marasmus and 10 ml/kg for KWO.
- Fresh packed RBCs for severe anemia with anemic heart failure:
10 ml/kg for marasmus and 5 ml/kg for KWO

III. Dietetic treatment**Route**

- Preferably oral
- Nasogastric tube for cases with severe anorexia

Amount

- Start at 80-100 cal./kg/day in stabilization phase
- Increase gradually in *Rehabilitation phase* (2nd - 6th week) to a target of 150-220 kcal/kg/d
- Fluid 130 ml/kg/d (100 ml/kg/d if the child has severe edema) of low osmolality and low lactose feeds
- Small frequent feeds every 2-3 hours day and night increased gradually over 1-2 weeks in strength & amount as the appetite improves

Protein intake

- Start with 1-1.5 gm/kg/d and increase gradually to 4- 6 gm/kg/d

Type of food

- If the child is breastfed, encourage to continue breastfeeding but give the prescribed amounts of starter formula (F-75) to make sure the child's needs are met
- Severe malnutrition between 6 – 60 months of age benefit from
Powdered milk–based foods (Formula diets)
 - F75 (75 cal/100ml without iron) for initial feeding.
 - F100 (100 cal/100ml with iron) is used later in the rehabilitation phase
- Ready to use therapeutic foods (RUTF)**
 - A mixture of powdered milk, peanuts, sugar, vitamins, and minerals
 - Much better than formula diets

III. Supportive treatment**1. Multivitamins especially**

- Thiamin / Vitamin B complex, Vitamin A
- Vitamin D: prevents rickets during period of catch up growth.

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2. Minerals especially

- Phosphorus
- Magnesium
- Calcium
- Zinc and Copper
- Iron (should be used after the first week of treatment).

3. Plasma or albumin for KWO.

IV. Treat of the cause in secondary marasmus

VI. Follow up phase last from 7th week to 26th week

- For feeding to cover catch-up growth
 - High protein diets: eggs, chicken, meat, fish, yogurt, cheese, beans, & lentils.
 - High caloric diets e.g. potatoes, rice
- Providing emotional and sensory stimulation
- Weight gain of 15% is a marker for discharge from hospital

Refeeding syndrome

Definition

- Potentially fatal condition caused by rapid initiation of refeeding after a period of undernutrition (during the 1st week of starting to refeed)
- Hypophosphatemia is the hallmark of this disorder
- Rapid feeding \Rightarrow hyperinsulinemia \Rightarrow intra cellular shift of phosphate , potassium ,and magnesium along with salt retention and hyperglycemia

Clinically

- Cardiac: hypotension, arrhythmias
- Respiratory failure
- Neurologic : weakness and paralysis, altered mental status, seizures
- Rhabdomyolysis
- Sudden death

Prevention/treatment

- Give Thiamin 200-300 mg daily oral plus other B complex vitamins
- Start feeding very slow and advance more slowly
- Rehydrate carefully with ReSoMal which has higher potassium & less sodium
- Supplement and or correct levels of phosphate, potassium, calcium & magnesium

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Minerals Requirements

	Calcium	Iron	Magnesium	Phosphorus
Daily need	800mg	10-15 mg	100 mg	600 mg
Sources	- Milk, cheese - green vegetables	- Liver, meat - Vegetables, apple	- Milk, meat - cereals, legumes	- Milk, proteins, milk products
Functions	- Bone & teeth - Muscle contraction - Nerve transmission - Blood coagulation - Cardiac action	- Haemoglobin. - Myoglobin. - Oxidative enzymes as catalase & cytochrome oxidase	- Bone & teeth - Conversion of proparathormone to parathormone	- Bone & teeth - Structure of muscles - CHO and fat metabolism
Deficiency	- Rickets - Tetany - Delayed teething	- Iron deficiency anaemia	- Tetany; associated frequently with hypocalcemia	- Rickets

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الدفعه ال14

Water Soluble Vitamins

Criteria

- Include vitamins B complex and C
- Not stored in the body so not toxic
- Therapeutic trial → give dramatic response
- When treating one vitamin deficiency, consider supplying other vitamins as well
- Rich diet: liver, meat, milk, eggs, vegetables, cereals, poultry, fish, whole grains

Vitamin B₁ (Thiamine) deficiency

Beri Beri

1. Early ⇒ Fatigue, insomnia, anorexia



2. Dry Beri Beri

- Polyneuropathy
- Dysphonia (recurrent laryngeal nerve paralysis)
- Ataxia, and psychosis (Wernick's Korsakoff syndrome).

3. Wet Beri Beri → Cardiomyopathy → congestive heart failure with generalized edema

Treatment - B₁ 10 mg IM daily (consider supplying other vitamins)

Vitamin B₂ (Riboflavin) deficiency



a. Cheilosis, angular stomatitis, glossitis



b. Keratitis and corneal vascularization
→ Photophobia

Treatment - B₂ 10 mg IM daily (consider supplying other vitamins)

Vitamin B₃ (Nicotinic acid, Niacin) deficiency



Pellagra (*pellis* = skin, *agra* = rough)

1. Dermatitis

- In sun exposed areas (hands, feet, head & neck).
- Erythema, scales, crusts & desquamation
- Sharply demarcated borders

3. Diarrhea - With stomatitis, cheilosis & glossitis

4. Dementia - Apathy.

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- Treatment
- Vitamin B₃ 50-300 mg daily
 - Avoid maize (poor in tryptophan).

Vitamin B₆ (pyridoxine) Deficiency

1. Infantile convulsions
 - Why ? B₆ is essential for synthesis of inhibitory neurotransmitter; GABA.
 - Nature? Myoclonic type
2. Anemia
 - Why ? Failure of heme synthesis due to failure of iron utilization.
 - Nature? Microcytic hypochronic.
3. Peripheral neuropathy
 - In patients on INH therapy
4. Skin
 - Cheilosis and seborrheic dermatitis

- Diagnosis
- Therapeutic trial with 100 mg IM in convulsions

- Treatment
- For pyridoxine dependent child 10-100 mg oral daily
 - Diet with rich sources as for vitamin B₃ & soybeans

Vitamin C (Ascorbic acid)

- Value
- Synthesis of collagen.
 - Necessary for folic acid and iron absorption.

Deficiency

- 1- Bone tenderness mainly in legs → pseudoparalysis.
- 2- Bleeding: subperiosteal hemorrhages, swollen bleeding gums & purpura.
- 3- Scorbutic rosary Beads :
 - At costo chondral junctions.
 - Sharply angular, tender, irregular.
 - With sternal depression.
- 4- Follicular hyperkeratosis(Papular skin)
- 5- Poor wound healing
- 6- Pallor due to (hemorrhagic, folic acid deficiency, iron deficiency) anemia



- Treatment: Citrus fruits & vitamin C tablets 100-200 mg daily.

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Fat Soluble Vitamins

Stored in the body so may be toxic

Vitamin E deficiency

- Functions**
- Cell membrane stabilizer
 - Anti oxidant
- Causes**
- Fat malabsorption, malnutrition & prematures
- Deficiency**
- Hemolytic anemia in preterm
 - Ataxia.

Vitamin A deficiency

- Functions**
- Retinal function (responsible for night vision)
 - Integrity of epithelium (of skin and mucosa)
- Deficiency**
- Night blindness(hard to prove in infancy)
 - Eyes → Bitot spots, xerosis, keratomalacia & corneal ulceration.
 - Respiratory, gastro intestinal and urinary infection.
 - Perifollicular keratosis (Toad s skin)

Toxicity

1. Acute: Due to ingestion of single massive dose.
 - Increased intracranial pressure (vomiting, headache, bulging fontanel)
 - Resolve spontaneously
2. Chronic: Due to large daily doses for weeks to months

Skin

- Alopecia
- Pruritus.
- Carotenemia (yellow skin)
- Desquamation of hands and feet

Bone

- Cranio**t**abes
- Metaphyseal Deformities

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Self Assessment Case Scenarios

Case 1

A 10-month-old infant presented to the ER with bilateral edema of the lower limbs and pallor. His mother gave a history of recurrent attacks of vomiting and diarrhea. On examination: wt 5.5 kg, pitting edema of both lower limbs, wasting of the muscles of the thigh and ulceration in the buttocks. Abdominal examination revealed enlarged liver 3cm below the costal margins, firm consistency.

a. What is the probable diagnosis?

b. Discuss dietetic management?

Case 2

A 12 months old boy, He was one of twin whose birth weight was 1.700 gm and now he is 4.200 gm. He was given exclusive breast-feeding without any supplementations. The mother was always complaining from insufficient milk in her breast. Examination reveals alert, irritable, crying infant with skin over bone appearance; no other systemic illness

a. What is the underlying disease?

b. What are the possible 4 risk factors for the existing disease?

Case 3

A 1.5 years old female whose mother complains that she is not gaining weight .History reveals that the baby has not been interested in feeding since she was 2 months old ;she got tired easily during breast feeding with marked tachypnea ,tachycardia and sweating. On examination: weight 4 kg,(birth weight was 3 kg) , MAUC 11cm , wasted buttocks but no edema. She is alert, tachypneic , tachycardic ,with soft ejection systolic murmur over pulmonary area and clearly audible second heart sound

a. What type of malnutrition in this case?

b. What is the cause of malnutrition in this case?

c. What are the investigations required to confirm it?

d. What should be lines of treatment for this condition?

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Vitamin D Metabolism

Daily requirement: 400 IU/day if <1 yr old and 600 IU/ day if >1 yr old (mainly for breast milk feeders). For Preterm baby \Rightarrow 1000 IU/d

Metabolism

- ③ Ultra violet rays convert
7- Dehydrocholesterol in the skin
to vitamin D_3



- ④ In the liver: Vitamin D_3 is converted to $25(OH)D_3$ by 25 hydroxylase enzyme.

- ① There's two forms of vitamin D
- $D_2 \rightarrow$ ergocalciferol \Rightarrow plant origin.
 - $D_3 \rightarrow$ cholecalciferol \Rightarrow animal origin.

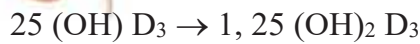


- ② Vit D is absorbed from the upper small intestine with aid of bile salts.

If

- Low serum calcium or phosphate
- High parathyroid hormone level

1 α hydroxylase enzyme is activated.



Active form

Functions

Via synthesis of transport protein



- Enhance Ca. phosphate deposition in bones.

\Leftarrow Ca: Ph ratio
2 : 1



- \uparrow Renal reabsorption of calcium & phosphate

+



- \uparrow Intestinal absorption of calcium & phosphate

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Vitamin D disorders

Hypervitaminosis D

(Vitamin D intoxication)

Excessive prolonged unmonitored vitamin D intake

Clinical picture

Manifestations are due to hypercalcemia:

System	Manifestations
1. Gastro intestinal	- Vomiting, and constipation - Acute abdominal pain (pancreatitis or peptic ulcer)
2. Renal	- Polyuria, polydipsia and dehydration - Nephrocalcinosis and renal stones
3. Cardiovascular	- Hypertension - Aortic valve stenosis
4. Neurologic	- Lethargy, and coma (pseudotumor cerebri) in severe cases

Prevention

- Monitor serum calcium for cases treated with large doses of vitamin D;
if > 11 mg /dl; stop vitamin D

Investigations

- Serum calcium > 11 mg /dl → Suppressed PTH and hypercalciuria
- Hyperphosphatemia
- Elevated levels of 25-D (>150 ng/mL)
- Surprisingly, levels of 1,25-D are usually normal. This may be a result of downregulation of renal 1 α -hydroxylase by the combination of low PTH, hyperphosphatemia
- Radiologic: Nephrocalcinosis often visible on ultrasound or CT scan

Treatment

1. Stop	- Calcium & vitamin D intake - Sun exposure
2. Correct	- Dehydration
3. Enhance urinary calcium loss	- Saline infusion plus Furosemide
4. Reduce calcium absorption	- Prednisone (the best) - Cholestyramin
5. Shift calcium to bones	- Calcitonin
6. Severe hypercalcemia	- Hemodialysis using low or 0 dialysate calcium

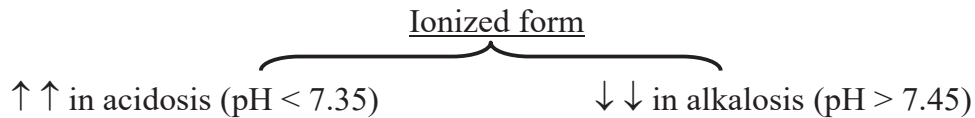
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Important Notes

- ❶ Normal serum calcium (Ca) = 9 – 11 mg/dl.
 Normal serum phosphate (Ph.) = 4.5 – 5.5 mg/dl.
 So, Ca: Ph. ratio in blood = 2:1 which is optimal for absorption & mineralization of bones

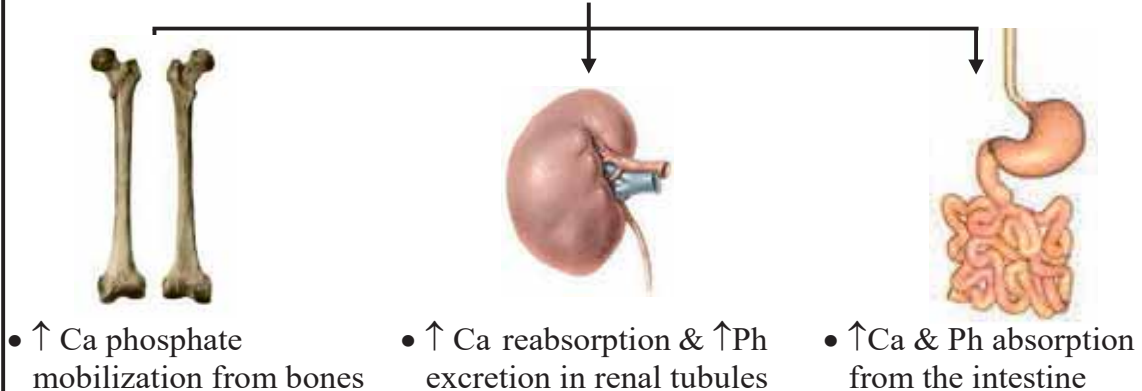
- ❷ Production of Ca × phosphate usually constant $\approx 40 - 50$ this product is called Holland formula **or** solubility product.
 * If serum phosphate increases \rightarrow reciprocal decrease in serum Ca occur to keep the formula constant.
 * If Holland formula $> 80 \Rightarrow$ widespread deposition of Ca phosphate occur in different tissues (metastatic calcifications) especially in the kidneys & heart.

- ❸ Serum Ca has 2 forms in balance:
 * Non ionized form \rightarrow inactive
 * Ionized form \rightarrow active form.



- ❹ **Parathyroid (Parathormone) hormone (PTH)** is secreted from parathyroid glands
- Main action of PTH is to keep serum calcium constant.
 - \downarrow Serum Calcium **or** \uparrow Serum phosphate stimulate parathyroids $\Rightarrow \uparrow$ PTH \Rightarrow Secondary hyperparathyroidism (2^{ry} HPT).

Actions



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Tetany

Definition: A state of hyper excitability of the central & peripheral nervous system.

Causes

1- Hypocalcemia Due to

- Decreased calcium intake
- Hyperphosphatemia (common in cow milk feeders)
- Magnesium (Mg) deficiency: Mg is essential for parathormone synthesis
- Hypertonic dehydration
- Vitamin D deficiency & hypocalcemic rickets.
- Hypoparathyroidism.
- Acute pancreatitis



2- Alkalosis (Decreases ionized calcium) Due to

- Loss of HCL due to repeated vomiting.
- Excess alkali intake.
- Bartter syndrome.

3- Hypomagnesemia (N = 1.5 – 2.5 mg/dl).

Clinical picture

A . Latent tetany

With serum calcium 7 – 9 mg/dl; detected by:

<p><u>Chevostek sign</u> Tapping the facial nerve in front of the ear → twitch of the mouth</p>	<p><u>Trousseau sign</u> Inflation of sphygmomanometer cuff over the arm above systolic pressure for 3 min ⇒ <i>carpal spasm</i></p>	<p><u>Peroneal sign</u> Tapping of the peroneal nerve → dorsiflexion + abduction of the foot</p>	<p><u>Erb's sign</u> Motor nerve can be stimulated by low current</p>

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B. Manifest Tetany**With serum calcium < 7 mg/dl ; manifested by :**

1. Carpo pedal spasm:
 - Flexion of the wrist & metacarpophalangeal joints
 - Extended interphalangeal joints
 - Flexed adducted thumb.
 - Plantar flexion & inversion of the feet
2. Laryngeal spasm (laryngismus stridulous): stridor is afebrile & recurrent.
3. Convulsions: generalized, recurrent, and baby is conscious between attacks

**Investigations**

For hypocalcemia	For hypomagnesemia	For alkalosis
* Serum Ca (Total & ionized)	* Serum magnesium	* Blood gases(pH)
* Serum inorganic phosphorus		
* Serum parathyroid hormone.		

Treatment**A- Hypocalcemic tetany****1. Acute attack**

- Immediately relieve hypocalcemia by intravenous calcium
- Dose: 1- 2ml/kg of calcium gluconate 10%
- Slow infusion over 5-10 minutes with cardiac monitoring
- May repeat at 6 hourly until serum calcium level stabilizes.

2. Once symptoms of hypocalcemic tetany have resolved

- Oral calcium 50 mg /kg tapered over 2-6 wk
- Encourage calcium rich diet

3. Vitamin D therapy

- Is started after control of the acute attack
- For hypocalcemia with rickets → oral calcium & vitamin D till healing
- For hypoparathyroidism → oral calcium & active vitamin D

B- For hypomagnesemia

- Mg sulphate 50%
- Dose: 0.2 ml/kg I.V, I.M or oral

C- For alkalosis

- Metabolic alkalosis: Adequate sodium and potassium intake
- Respiratory alkalosis: Re-breath into bag to ↑ PaCO₂

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Rickets

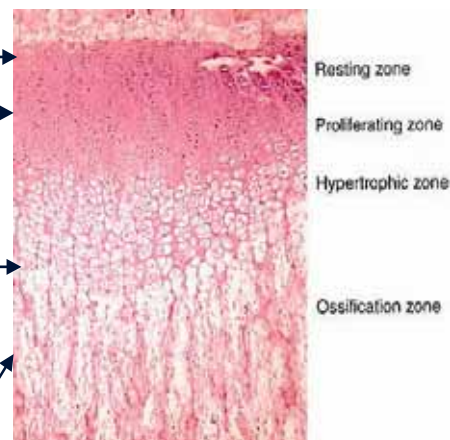
Definition

Metabolic bone disease due to failure of mineralization of osteoid tissue of the growing bones due to either:

- Defective intake or metabolism or function of vitamin D.
- Inappropriate calcium / phosphate ratio (usually due to hypophosphatemia, rarely due to calcium deficiency)

Normal bone ossification

- Resting zone: single layer of cartilage cells →
- Proliferating zone: Regular avascular cartilage →
- Normal zone of provisional calcification → continuous line in ends of long bones → radiographs
- Osteoblasts lay osteoid and secrete alkaline phosphatase
- Ossification of osteoid in presence of normal vitamin D & calcium phosphate ratio



In Rickets

- Irregular very vascular *excessive* cartilage (felt clinically)
- Absent zone of provisional calcification → fraying of the ends of the long bones in (radiographs)
- Osteoblasts lay *excessive* osteoid and secrete *excessive* alkaline phosphatase (laboratory)
- Poor ossification of osteoid in *absence* of normal vitamin D *or* calcium phosphate ratio → weak non rigid bone → bone yield under pressure → cupping, broadening, deformities and fractures (clinical/radiographs)

So

Rickets is basically suspected clinically and confirmed with both bone radiograph and laboratory

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Classification of rickets

Type of rickets	Serum calcium
<u>Calcium deficiency with 2^{ry} hyperparathyroidism</u> <ol style="list-style-type: none"> 1. Nutritional vitamin D deficiency (Infantile rickets) 2. Secondary vitamin D deficiency due to: <ul style="list-style-type: none"> ○ Malabsorption syndromes (Celiac rickets). ○ Decreased liver 25-hydroxylase activity in chronic liver disease ○ Increased degradation e.g. with anti epileptic drugs. 3. Rickets with chronic renal failure (Renal osteodystrophy) 4. Vitamin D dependent rickets type I 5. Vitamin D dependent rickets type II 6. Calcium deficiency : nutritional , malabsorption or in premature infant 	Normal <u>Or</u> Low
<u>Phosphate deficiency without 2^{ry} hyperparathyroidism</u> <ol style="list-style-type: none"> 1. Decreased phosphate intake <ul style="list-style-type: none"> • Premature infants (rickets of prematurity) 2. Renal phosphate losses e.g. <ul style="list-style-type: none"> • Familial hypophosphataemia. • Fanconi syndromes • Overproduction of phosphatonin e.g. Tumor-induced rickets 	Normal

Causes of rickets other than nutritional rickets are referred to as: Non vitamin D deficiency rickets (or Vitamin D refractory or resistant) as they are not cured with the same dose or form of vitamin D that cures nutritional rickets

(Nelson Textbook of pediatrics)

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Vitamin D Deficiency Rickets

Predisposing factors

- Season : - Commoner in winter
 Age : - Commonest age → 6 months - 24 month.
 Growth : - More in rapidly growing infant e.g. twins & preterm.
 - Less in infants with arrested growth e.g. PCM & cretinism.

Etiology

A. Decreased vitamin D intake due to:

1. Lack of rich sources of vitamin D e.g. egg yolk, meat, fortified milks, fish liver oil.
2. Use of rachitogenic diet with:
 - Poor sources of vitamin D as fresh animal milk ,cereals and carbohydrates.
 - Poor sources of calcium as cereals ,and excess leafy vegetables
 - Inappropriate calcium /phosphate ratio as in fresh animal milk

B. Lack of access of ultra violet rays to the skin due to:

1. Lack of sun exposure
2. Poor sun exposure through glass windows, clouds & dust.
3. Excessive wrappings of the infants.
4. Poor penetration in dark skinned infants

Clinical picture

I. Early Rickets

- 1- Anorexia, irritability, & sweating of forehead

2- Craniotables

- Skull bones yield under pressure →
Ping - pong or egg shell crackling sensation.
- Due to thinning of inner table of the skull
- Disappear by the end of 1st year.
- Detected by pressing over occipital or parietal bone



- 3- Rachitic rosaries: palpable enlargement of costochondral junctions (excess osteoid)

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II. Advanced Rickets

i. Skeletal Changes

1. Head

- Large head
- Large anterior fontanel (delayed closure).
- Asymmetric skull; may be box shaped

- Frontal & parietal bones bossing due to excess osteoid
- Depressed nasal bridge
- Delayed teething, dental caries



2. Chest



- Rachitic rosaries
 - Visible & Palpable.
 - Rounded, Regular, Non tender



- Longitudinal sulcus → lateral to the rosaries
- Harrison sulcus → transverse groove along the costal insertion of the diaphragm
- Chest deformities:
 - * Pigeon chest → sternum & adjacent cartilages project forwards.
 - * Funnel chest → depression of the sternum & flaring out of the lower ribs.

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3. Vertebral column : there may be

- a. Kyphosis: in dorsolumbar region
 - Smooth.
 - Apparent on sitting, disappear by lifting.
 - With compensatory lumbar lordosis
- b. Scoliosis: lateral curvature of the spine

4. Extremities



a. Broadening of epiphysis of long bones especially at wrist & ankles.

b. Marfan sign: transverse groove over the medial malleolus due to unequal growth of the two ossific centers.



c. Deformities: Due to weight bearing on the soft bones;

* Crawling infants:

- Bowing of forearm
- Anterolateral curvature of femurs
- Anteroposterior curvature of legs

* Walking child:

- Bow legs (Genu varus)
- Knock knees (Genu valgum)
- Overextended knees (Genu recurvatum)



ii. Non Skeletal Manifestations

Manifestations:

- 1- Delayed motor milestones.
- 2- Abdominal distension (pot belly abdomen) ; with or without umbilical hernia
- 3- Ptosis of the liver & the spleen (also due to chest deformities).
- 4- Constipation → due to intestinal hypotonia.

Etiology: - Hypotonia of skeletal muscles (due to hypophosphatemia)
 - Laxity of ligaments

Complications

- 1- Respiratory infections & atelectasis due to:
 - a- Limited chest expansion.
 - b- Hypotonia of respiratory muscles → weak cough reflex.
- 2- Gastroenteritis due to intestinal hypotonia → stasis → 2^{ry} bacterial overgrowth.

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- 3- Tetany : may occur in rickets with hypocalcaemia
- 4- Skeletal deformities: - Mild and early managed cases → reversible.
- Advanced and neglected cases → permanent.
- 5- Disproportionate short stature (Rachitic dwarfism)→ due to deformities of spine, pelvis & limbs
- 6- Iron deficiency anemia is a common association (Von-Jack anemia = anemia , rickets , lymphadenopathy and splenomegaly)

Investigations

I. Biochemical

- Serum calcium is normal, but may be low (normal = 9 – 11 mg/dl).
- Serum inorganic phosphorus (Ph.) is low (normal value = 4.5 – 6.5 mg/dl).
- Serum Calcium × Phosphate product is low (less than 30).
- Serum alkaline phosphatase enzyme (Alk. Phos.):
 - High
 - The most sensitive indicator of rachitic activity; due to osteoblastic activity
 - Return to normal after complete healing of rickets.
- Serum Parathyroid hormone (PTH) → high.
- Serum 25 (OH) D₃ → low
- Serum 1.25 (OH)₂ D₃ → low in severe vitamin D deficiency

Explanation: ↓ 1,25 (OH)₂ D₃ → ↓ calcium absorption → serum calcium tend to be low → ↑ PTH → ↑ calcium & ph. mobilization from bones + ↑ ph. loss in urine → normalized serum calcium + ↓ serum ph.

However hypocalcemia (and may be tetany) may occur with:

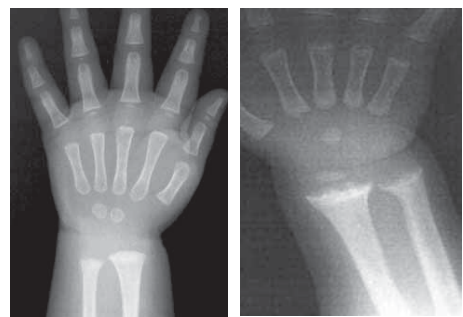
- 1- Failure of 2nd hyperparathyroidism to occur.
- 2- In advanced cases with depletion of bone calcium.
- 3- Shock therapy → ↑↑↑ deposition of calcium Ph. in bone on the expense of serum calcium which may fall below normal.

II. Radiologic: by X-ray at lower ends of long bones especially wrist due to easy access , rapid growth and soft tissue around is thin.

a. Active rickets

The lower ends show

- Broadening ; widening of the distal end of the metaphysis
- Cupping or concavity ; metaphysis changes from a convex or flat surface to a more concave surface
- Metaphysis loses its sharp border (Fraying)
- Wide joint space



Normal wrist

Rachitic wrist

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The shaft shows

- Rarefaction → ↓ bone density
- May be green stick fracture.
- May be deformities

**b. Healing rickets**

- Usually seen 2 weeks of vitamin D therapy
- The lower ends shows white concave continuous line at ZPC
- Less evident features of rickets

**c. Healed rickets**

- Usually seen 4 - 6 weeks of vitamin D therapy
- The lower ends show straight continuous line at ZPC.
- No features of active rickets.

Differential diagnosis from other causes of :

1. Non vitamin D deficiency rickets
2. Delayed motor milestones e.g. Inability to walk
3. Craniotabes which may occur in:
 - Premature → disappear by the 3rd month
 - Hydrocephalus → weakness affect all bones
 - Osteogenesis imperfecta → weakness since birth
 - Congenital syphilis.
4. Pott's disease (T.B of spine): - Kyphosis is angular & persistent.
- X-ray and CT spine is diagnostic.
5. Rosary beads:
 - a. Scorbutic Rosaries: Due to deficient collagen → subperiosteal hemorrhage
Criteria:
 - At costo chondral junctions.
 - Angular, tender, irregular.
 - With sternal depression.
 - Associated with other clinical features of scurvy
 - c. False Rosaries in marasmus : Prominent normal costochondral junctions

N.B. Atrophic rickets

- Rickets in non growing bones as in protein calorie malnutrition
- Absent osteoid overgrowth signs i.e. No bossing , wrist or ankle broadening , rachitic rosaries nor Marfan sign.
- Other signs of rickets are present e.g. wide fontanels, hypotonia,.....

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Treatment

1. Prevention

- a. Vitamin D supplement usually as daily multivitamin

Dose: - For less than 1 year → 400 IU/day mainly for Breast feeders
- For above 1 year → 600 IU/day

- b. Advice for:

- Exposure of pregnant mothers and infants to sunlight
- Diet with adequate calcium and phosphorus(formula, milk , dairy products)
- Vitamin D and calcium supplement for pregnant and lactating mothers

2. Curative

- a. Vitamin D₃:

- * Oral : 2000 – 5000 IU/day for 4 - 6 weeks
- * Stoss (Shock) therapy :
 - 300.000- 600.000 IU IM or oral for 2-4 doses over 1day
 - Indicated if compliance is uncertain

Either strategy should be followed by daily vitamin D intake maintenance

- b. Advice parents for:

- Advice about Diet and sunlight as before
- Avoid weight bearing in infants during active rickets.

- c. Treat complications:

- * Tetany
- * Deformities: osteotomy and reconstruction if severe and persistent.

After 4- 6 weeks of treatment: Look for criteria of improvement;

1. Radiologic : Appearance of zone of provisional calcification is the earliest finding.
2. Laboratory : Normalization of alkaline phosphatase indicates complete healing
3. Clinical: Improved muscle tone but skeletal manifestations may take a longer time
(Some skeletal signs may persist as large head , severe deformities, pigeon chest)

Decision: Reduce vitamin D dose to the normal daily requirement (to avoid toxicity)

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Other Hypocalcemic Rickets

1. Rickets with malabsorption



- Clinical and lab features of malabsorption
- +
- Clinical , lab and radiologic features of infantile rickets

Treatment: Treat malabsorption syndrome + 25 OH D3 or calcitriol (Better absorption) or Parenteral Vit D

The dose is adjusted based on monitoring of serum levels of 25-D

2. Rickets with chronic liver disease



- Clinical features of chronic liver disease → jaundice, bleeding, edema
- Lab features of chronic liver disease → Raised bilirubin , liver enzymes , prolonged PT , low albumin

+

- Clinical , lab and radiologic features of infantile rickets

Treatment : Treat chronic liver disease + 25 OH D3

3. Rickets with anti epileptic drugs



- Prolonged anti epileptic medicines (phenytoin , phenobarbitone or carbamazepine) → enzyme inducers → inactivation of 25 (OH) D₃
- Poor sun exposure or poor diet in neurologically disabled

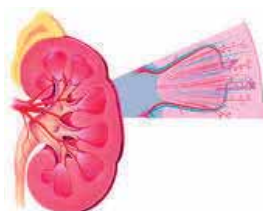
+

- Clinical , lab and radiologic features of infantile rickets

Treatment: Oral calcium+ Sun exposure + 25 OH D3

Prevented by extra dose of vit D for all susceptible epileptics

4. Vitamin D dependent rickets type I



- Autosomal recessive defect in 1 α hydroxylase enzyme
- Clinical , lab and radiologic features of infantile rickets

But

- Develop early in life
- Serum vitamin D: Normal 25 OH D3 / Low 1,25 (OH)₂ D3

Treatment: Oral calcium + 1,25 (OH)₂ D3 (**R/Calcitriol**)

Monitor urinary calcium excretion, with a target of <4 mg/kg/day

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5. Vitamin D Dependent Rickets Type II



- Autosomal recessive end organ resistance to $1,25(\text{OH})_2\text{D}_3$
- Clinical, lab and radiologic features of infantile rickets

But

- Develop very early in life
- Serum vitamin D: Normal $25(\text{OH})\text{D}_3$ / High $1,25(\text{OH})_2\text{D}_3$
- Associated with short stature and alopecia totalis (severe)

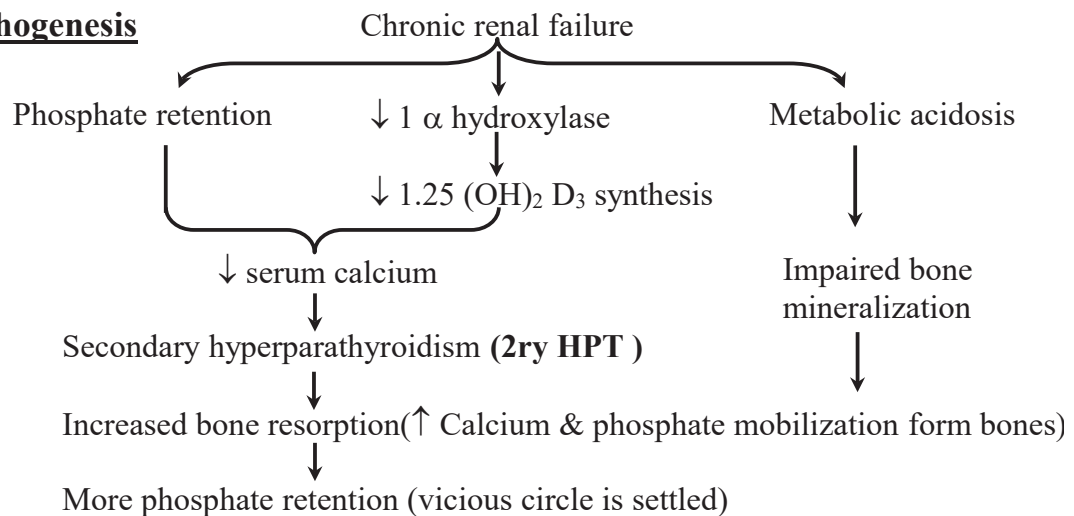
Treatment: Oral calcium+ Calcitriol high dose may be of value

A trial period of 3-6 months with this regimen is initiated

Monitor urinary calcium excretion, with a target of $<4\text{ mg/kg/day}$

6. Renal Osteodystrophy (ROD) (Renal Glomerular Rickets)

Pathogenesis



Clinical picture

a. Features of chronic renal failure (anorexia, anemia, growth failure, hypertension, ...)

b. General features of rickets but:

- Deformities & fractures are very common due to combined effect of rickets & secondary hyperparathyroidism.
- Tetany is rare → as metabolic acidosis ↑↑ ionized Ca
- Bone pain and muscle weakness in older children.

Investigations

1- Biochemical:

Ca	Ph.	PTH	ALK phos.	$25(\text{OH})_2\text{D}_3$	$1,25(\text{OH})_2\text{D}_3$
Normal or ↓	↑↑	↑↑	↑	Normal	↓

- Evidence of renal failure (↑urea & creatinine), and anemia
- Urinary phosphate is low unlike other types of rickets

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2- Radiologic

* General radiological features

- * Evidence of secondary hyperparathyroidism:
 - Subperiosteal erosions of bones
 - May be bone cysts \Rightarrow osteitis fibrosa cystica.



Management

A- Treatment of CRF \rightarrow conservative treatment with or without dialysis.

B- Treatment of ROD in the following steps guided by target level of PTH as decided by stage of renal failure:

1. Low phosphate diet (consult dietician).
2. Oral phosphate binders \rightarrow Calcium carbonate (calciolate) or
 \rightarrow Calcium acetate or
 \rightarrow Non calcium based binders (sevelamer; Renagel)
3. Correct chronic metabolic acidosis by sodium bicarbonate tablets
4. Oral One alpha [1α (OH) D₃] or calcitriol
- \downarrow
5. Calcimimetic drugs e.g. Cinacalcet can suppress hyperparathyroidism without inducing hypercalcemia
- \downarrow
6. Partial parathyroidectomy for persistent hyperparathyroidism.

N.B. Congenital rickets

- Due to severe maternal vitamin D during pregnancy
- Presentation: a newborn with :
 - a- Classic rachitic changes
 - b- Hypocalcemic tetany
 - c- Intra uterine growth retardation
- Prevented by adequate prenatal sun exposure and vitamin D supply

N.B. Calcium deficiency rickets

Tend to present later than Vit D deficiency rickets ; namely after weaning from breast feeding. May be associated with Vit D deficiency
 Treated by supplemental calcium according to age

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Hypophosphatemic Rickets

Renal Tubular Rickets

Rickets develop with renal tubular disorders due to either.

- Phosphaturia → ↓ serum phosphate → serum Ca: Ph ratio become inappropriate for mineralization.
- Metabolic acidosis → ↑ bone resorption.

Types of renal tubular rickets:

- 1- Familial hypophosphatemia
- 2- Fanconi syndromes:
 - a. Primary
 - b. Secondary
 - Cystinosis (Lignac syndrome)
 - Oculo-cerebro-renal (Lowe's syndrome)
 - Galactosemia.
 - Out dated tetracycline , mercury poisoning
- 3- Renal tubular acidosis

1- Familial hypophosphatemia	2- Fanconi syndrome (Idiopathic type)
<u>Etiology</u> Sex linked dominant disorder Characterized by decrease renal tubular reabsorption of phosphate → loss of phosphate in urine	Autosomal recessive disorder due to multiple defects in proximal renal tubules with ↓ urinary reabsorption of phosphate, bicarbonate & amino acids and may be potassium & glucose → all are lost in urine
<u>Clinical picture</u> <ul style="list-style-type: none"> - Rickets appear during the 2nd year of life especially bow legs with waddling gait and short stature. - Delayed teething and tooth abscesses - No evident rosaries , muscle weakness nor tetany 	<ul style="list-style-type: none"> - Rickets (due to phosphaturia , acidosis) - Vomiting (due to acidosis) & constipation - Polyuria and polydipsia - Episodes of dehydration and fever - Muscle weakness - Growth retardation - May be renal stones (uric acid)
<u>Laboratory</u>	
• ↓ Ph. <u>Others:</u>	• Normal Calcium • No 2 ^{ry} HPT • ↑ Alk. Phosphatase • ↑ urinary Ph., bicarbonate & amino acids (may be potassium & glucose) • Metabolic acidosis
• Phosphaturia	

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Treatment

1. Oral phosphate 1 – 3 gm/day divided into 5 doses
2. Vitamin D:
 - Value :- Complete bone healing
 - Offset 2^{ry} HPT which usually accompany phosphate therapy.
 - Use: - Calcitriol (Calcitriol exerts negative feedback with PTH)
3. Oral bicarbonate for metabolic acidosis
4. Oral potassium for hypokalemia
5. Free access to water: 2-6 liters per day

(Nelson text book of pediatrics)

3- Lignac syndrome (cystinosis)

- ⊕ Autosomal recessive intra cellular storage disease characterized by deposits of cystine in lysosomes of liver, spleen, bone marrow, cornea & renal tubules → Fanconi like.



- Clinical and laboratory features of Fanconi

Plus

- Blond hair and fair skin
- Photophobia
- Untreated cases end in chronic renal failure by 10 years
- Elevated leucocyte cystine level
- Detect cystine crystals in cornea by slit lamp

- ⊕ Treatment: as Fanconi & mercaptamine (cysteamine) oral & eye drops.

4- Lowe's (oculo – cerebro – renal) syndrome

- ⊕ Sex linked recessive disorder of eyes, cerebral cortex & renal tubules → Fanconi like



- Clinical and laboratory features of Fanconi

Plus

- Eye → cataract & congenital glaucoma (Buphthalmos).
- CNS → mental retardation & hypotonia

- ⊕ Treatment: as Fanconi & treat associations

5- Renal tubular acidosis

- ⊕ Mainly proximal renal tubules defect → bicarbonaturia → Metabolic acidosis
- ⊕ Clinical picture, investigation & treatment → as Fanconi

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Conditions Resembling Rickets

1- Hypophosphatasia

- * Due to : Decreased serum alkaline phosphatase enzyme
- * Inheritance : Autosomal recessive disorders
- * There may be ↑ serum calcium
- * Treatment : No specific treatment ; some cases may benefit from fresh plasma

2- Metaphyseal dysplasia

- * Inheritance : - Autosomal dominant disorders
- * Forms : - Jansen type
 - Schmidt type
- * Clinical picture : - Short stature.
 - Bow legs with waddling gait.

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الدفعة الـ 14

Self Assessment Case Scenarios

Case 4

A 12 months old boy, presented to ER with severe respiratory distress. On examination he has severe stridor with suprasternal and substernal retractions, cyanosis, and disturbed conscious level. No history suggestive of foreign body inhalation. Further examination reveals broad wrists and ankles, plantar flexion of feet and abnormal posture of both hands.

- a. What is the complication and the underlying disease?
- b. What should be lines of treatment of presenting condition?

Case 5

A 14-month-old child has lower-extremity bowing, a waddling gait, genu varum, and is at the 5th percentile for height. Laboratory data include normal serum calcium, moderately low serum phosphate, and elevated serum alkaline phosphatase levels, hyperphosphaturia, and normal parathyroid levels.

What is the most likely diagnosis?

- A. Fanconi syndrome
- B. Genetic primary hypophosphatemia
- C. Malabsorption of vitamin D
- D. Phosphate malabsorption
- E. Renal osteodystrophy

Case 6

5-year-old girl is somewhat short and has mild leg bowing. Her medical history is significant only for well-controlled seizure disorder. Serum calcium, phosphorus, and alkaline phosphatase levels and urinary amino acid concentration are normal. A bone age is notable for abnormal distal radius and ulna mineralization.

Which of the following is the most likely diagnosis?

- A. Malabsorption syndrome
- B. Fanconi syndrome
- C. Genetic primary hypophosphatemia
- D. Rickets associated with anticonvulsive drug use
- E. Metaphyseal dysplasia

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الدفعۃ ال14

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الدفةة ال14



Genetic disorders

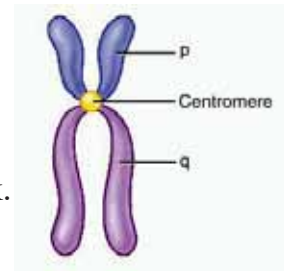
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الدفعۃ ال14

Basics of Genetics

Chromosome structure

- Each chromosome is composed of 2 chromatides
- The 2 chromatides are connected to at the centromere
- Each chromosome has 2 short arms (p) & 2 long arms (q)
- Each chromatide is composed of DNA in a protein framework.



Chromosomal number

1. **In somatic cells** : 46 chromosomes (i.e. diploid number) ; 44 autosomes & 2 sex chromosomes; X X in females & X Y in males
2. **In germ cells** : 23 chromosomes (i.e. haploid number); 22 autosomes & One sex chromosome(X in ovum and X or Y in sperm)

Mitotic Division

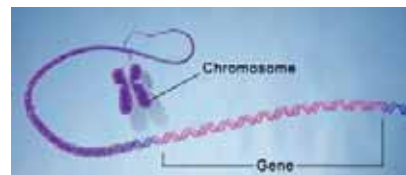
- Occur in all cells excepts CNS cells for renewal of cells & ↑number of cells
- **Steps** : Chromosomes arranged along the equatorial plane → Spindle protein fibers radiate from the centrioles to the centromeres → Each chromosome divide longitudinally into 2 daughter chromatids → Each set of chromatids moves to each pole of the cell → 2 daughter cells will form each contain 46 chromosomes (chromatids)

Meiotic Division

- Occur only in gonads for production of gametes (ova & sperms)
- Each gamete has a reduction of chromosomal number from 46 to 23
- **Steps**: Homologous chromosomes pair longitudinally (crossing over may occurs between 2 homologous chromatids) → Spindle connects centrioles to the centromeres → Homologous chromosomes separate randomly to each pole of the cell → production of 2 cells; each has haploid number of chromosomes → frequent mitosis follow on

Structure of the gene

- Part of DNA that code for synthesis of single polypeptide chain.
- Every trait (character or feature) is determined usually by 2 genes; one from each parent.
- If both genes are similar → Homozygous (e.g. AA or aa)
- If both genes are different → Heterozygous (e.g. A a)



- **Dominant gene** : Expresses itself whether in homozygous or heterozygous state
- **Recessive gene** : Expresses itself only when homozygous

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Each DNA is composed of

a- Sugar (deoxyribose) & phosphate backbone.

b- Nitrogenous bases:

- Pyrimidines : cytosine (C)&thymidine (T)

- Purines : adenine (A) & guanine (G).

* A always pairs with T.

* C always pairs with G.

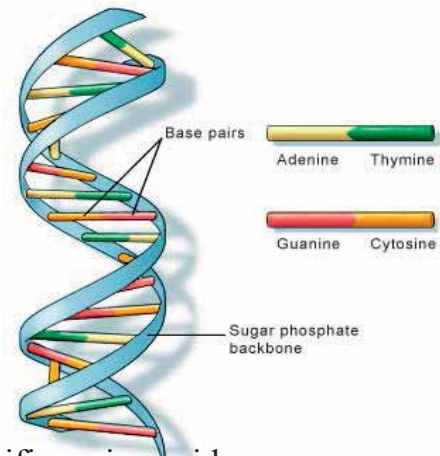
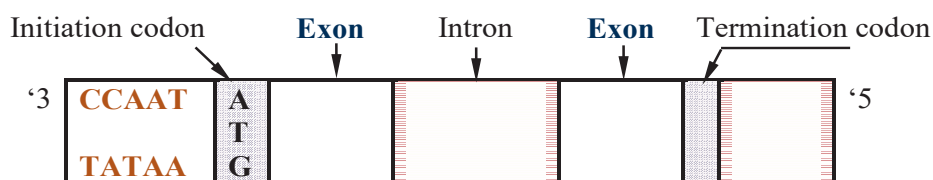
○ Nucleotide is a unit of :

- One deoxyribose

- One phosphate group

- One nitrogenous base

○ Each 3 successive nucleotides code for a specific amino acid

**Gene Expression****Human gene is composed of**○ **Exons:** Functional unit of gene sequences; coding for protein synthesis.○ **Introns:** Non coding DNA sequences of unknown function.○ **Initiation codon:** Specific sequence that determines initiation of protein synthesis.○ **Termination codon:** Specific sequences (TAA, TAG or TGA) which determine the end of transcription.○ **TATAA and CCAAT boxes:** Special sequences with unknown function, but may direct the enzymes for initiation sites.**Control of gene expression**

- Different cells have special functions due to different genes expression
- This can be achieved by methylation theory which states that: Parts of the gene which is methylated tend to be non-functioning and non-methylated parts tend to be functioning.

Types of DNA

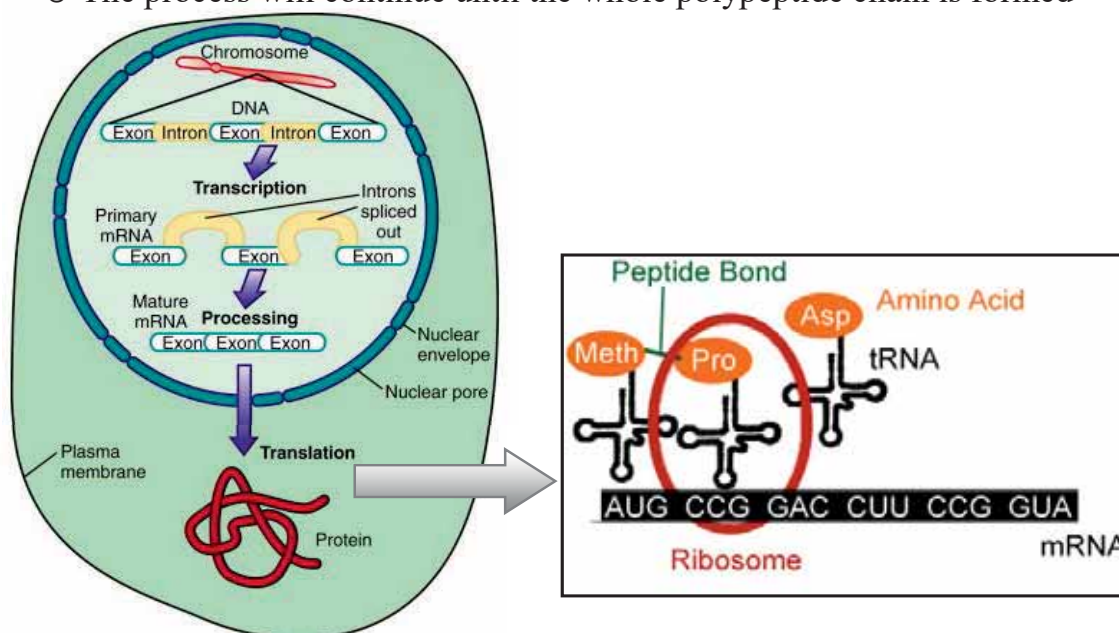
- **Non repetitive (unique) DNA** - Code for mRNA
- Involved in protein synthesis
- **Repetitive DNA** - Repeated DNA sequences
- Not coding for genes
- **Mitochondrial DNA** - Circular , maternally inherited
- 2-10 copies of double stranded DNA

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DNA functions

A. Protein synthesis (see the figure below)

- 1. Transcription:** synthesis of mRNA strand with the same sequence of DNA strand.
- 2. Processing:** the non coding segments (introns) of mRNA are removed and the remaining parts are joined together to form a functional mRNA
- 3. Translation**
 - mRNA leave the nucleus & attach to the ribosomes in the cytoplasm
 - When the ribosomal RNA comes in contact with that codon the tRNA with specific anticodon complementary to it comes in place, leaving the specific amino acid carried on it.
 - The mRNA moves and brings another codon in contact with ribosome.
 - Another tRNA comes in place and its amino acid attach to the first amino acid.
 - The process will continue until the whole polypeptide chain is formed



B. DNA replication (Duplication)

DNA can replicate itself (i.e. copy itself)

- **Aim**
 - DNA repair itself to replace a missed or broken segments after exposure to injurious agents e.g. irradiation
 - Formation of a complementary strand during cell division
- **How**

DNA helix split → form two single strands → pairing of the new complementary bases

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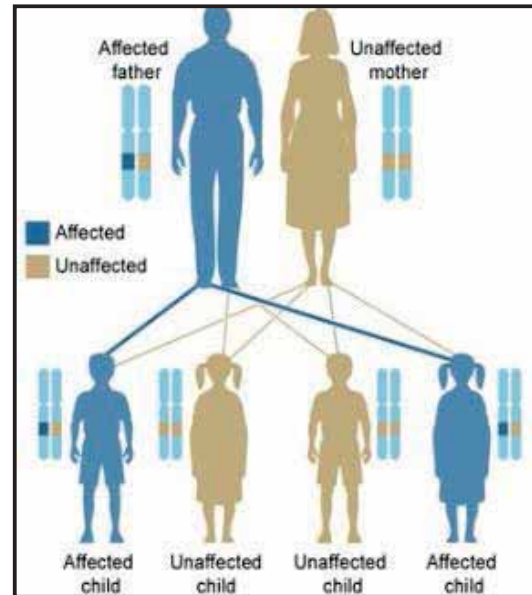
Modes of inheritance

i. Mendelian inheritance

1. Autosomal dominant (AD)

Criteria

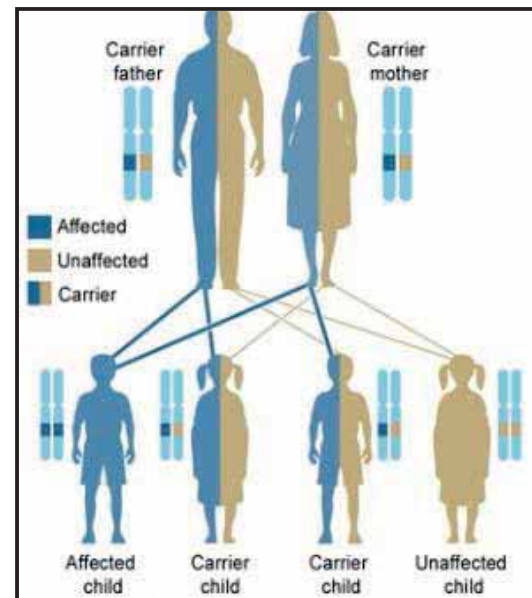
- The trait manifest in homozygous or heterozygous state
- Affected person has an affected parent (vertical transmission)
- Disease is transmitted from the affected person to $\frac{1}{2}$ of his offspring
- Disease appear in all generations
- New mutation is common
- Examples
 - Spherocytosis
 - Von Willbrand disease



2. Autosomal recessive (AR)

Criteria

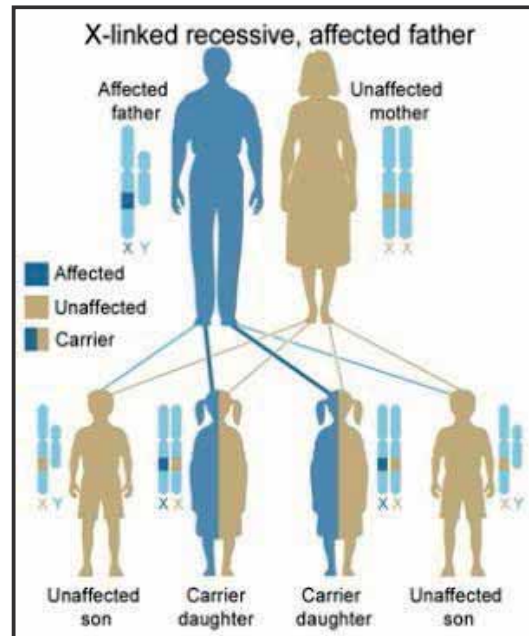
- The trait manifests only in homozygous state
- Both parents are carriers → Consanguineous marriage increase the incidence
- Offspring: $\frac{1}{4}$ free, $\frac{1}{4}$ affected and $\frac{1}{2}$ are carriers
- Examples
 - Thalassaemia
 - Inborn errors of metabolism e.g. phenylketonuria, albinism



3. Sex-linked recessive (XR)

Criteria

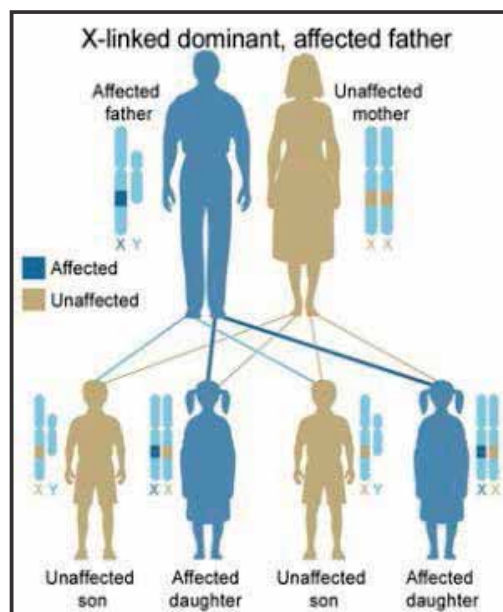
- Affect all males carrying affected gene while in females it appear only if homozygous
- Female carriers have $\frac{1}{2}$ of her sons affected and $\frac{1}{2}$ of her females carriers
- Affected father have all his females carriers but there is no father - son transmission
- Females may be affected if: affected male marry carrier female or female with only one copy of x chromosome (Turner) or due to Lyonisation(random inactivation of the sound X chromosome leaving the other X chromosome unopposed).
- Examples:
 - G6PD deficiency
 - Hemophilia A



4. Sex linked dominant (XD)

Criteria

- All persons -whether male or female- carrying the affected gene will express the trait
- Affected father transmit the trait to all daughters but never to his sons
- Affected mother transmit the trait to $\frac{1}{2}$ of her offspring whether males or females
- Example:
Familial hypophosphataemia



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ii. Non Mendelian modes of inheritance

A) Multifactorial inheritance

- * Caused by a combination of inherited and environmental factors
- * Risk of recurrence is increased when multiple family members are affected and when the disease is severe
- * Examples:
 - Cleft lip and cleft palate
 - Congenital pyloric stenosis
 - Diabetes mellitus



B) Non traditional modes of inheritance

1. Mitochondrial DNA mutations e.g. mitochondrial disorders

- Criteria
 - Maternally inherited but affect both sexes
 - Common manifestations:
 - Hypotonia, seizures, developmental delay
 - Deafness and impaired vision
 - Cardiomyopathy, diabetes mellitus

2. Genomic imprinting

- It is functional inactivation of a gene depending on the parent of origin
- Example: Prader Willi Syndrome/ Angelman Syndrome
 - Both syndromes are associated with loss of the chromosomal region 15q11-13
 - Paternal inheritance of a deletion of this region is associated with Prader Willi Syndrome
 - Maternal inheritance of the same deletion is associated with Angelman Syndrome

Prader Willi Syndrome	Angelman Syndrome
	
Mental retardation, hypotonia, hypogonadism, obesity, slender fingers and short stature	Mental retardation, gelastic seizures, fair skin and hair and global developmental delay

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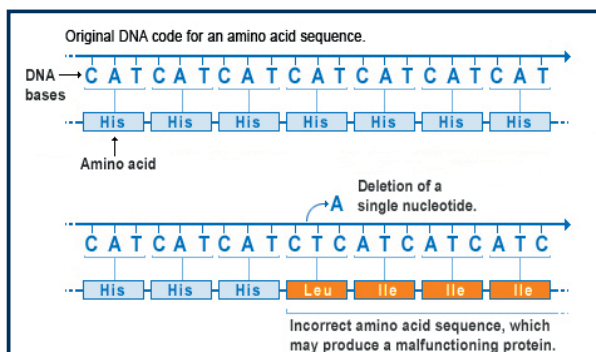
Mutation

Definition: A change in DNA sequence.

Types

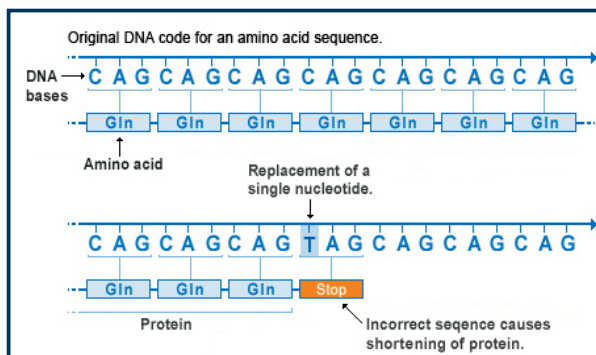
1. Deletion mutation

One nucleotide is deleted from the DNA code, changing the amino acid sequence that follows



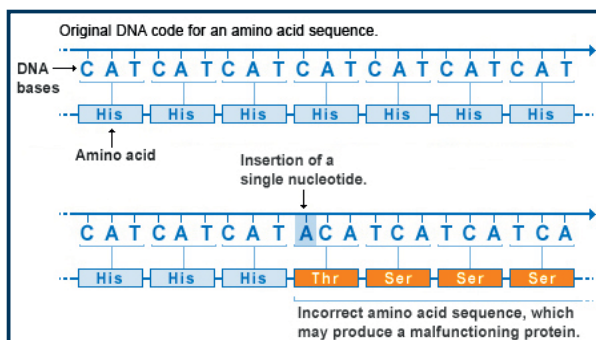
2. Insertion mutation

One nucleotide is added in the DNA code, changing the amino acid sequence that follows



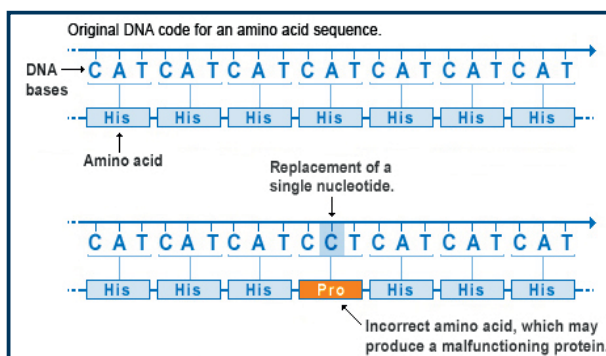
3. Missense mutation

A nucleotide is replaced by another one in the genetic code, introducing an incorrect amino acid into the protein sequence



4. Non sense mutation

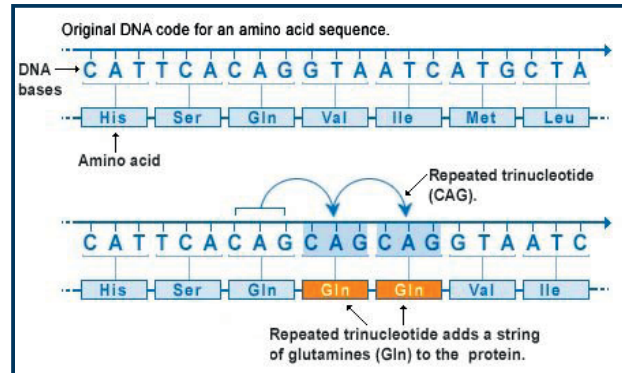
A nucleotide is replaced by another in the DNA code, signaling the cell to shorten the protein



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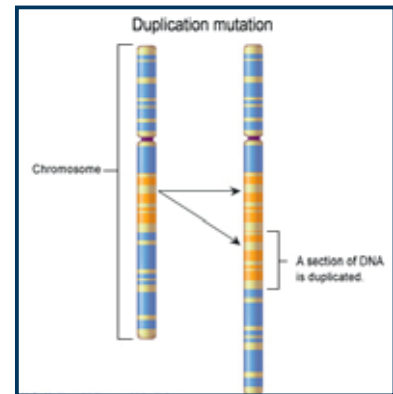
5. Tandem repeat mutations

- A repeated trinucleotide sequence adds a series of an amino acid to the resulting protein
- This expansion leads to gene
- Inactivation which increase with increase size of the repeats
- The disease increase in severity in subsequent generations
- Examples:
 - Fragile X syndrome (CGG nucleotide repeats)
 - Friedreich ataxia (GAA nucleotide repeats)



6. Duplication

A section of DNA is accidentally duplicated when a chromosome is copied



Outcomes of mutations

- Silent mutation
- Gain of function mutation:
 - Over expression of the gene product
 - Most are autosomal dominant disorders
- Loss of function mutations:
 - Under expression of gene → gene product is insufficient for normal functions
 - Most are autosomal recessive disorders.
- Mutations confer a novel property on the produced protein without altering the normal function e.g. sickle cell disease.
- Oncogenes: mutations affecting normal regulators of cellular proliferations causing cancer.

Diagnosis of mutation

By specific DNA probes using:

- Florescent In Situ Hybridization (FISH) technique or
- Polymerase Chain Reaction (PCR)

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Chromosomal Analysis(Karyotyping)

Karyotyping: Systematic arrangement of the chromosomes of a single prepared cell in pairs (according to the length) by photography

Preparation of study cells; cells can be obtained from:

1. Peripheral blood lymphocytes: Used for routine karyotyping.
2. Bone marrow: For rapid analysis and in leukemia.
3. Skin fibroblasts: In suspected mosaicism **or** if blood is not available
4. Amniotic fluid cells: Diagnose chromosomal anomalies in the 2nd trimester.
5. Chorionic villous sampling (CVS): Diagnose chromosomal anomalies in the 1st trimester (at 10-12 weeks).
6. Fetal cells in maternal blood analysis using FISH technique (Recent)

Techniques

1. G-banding

- * Chromosomes are stained in metaphase using Trypsin/Giemsa stain → examined under light microscope
- * Chromosomes appear as dark bands alternating with light bands.

2. High resolution banding

- * As G-Banding but each band is subdivided into sub bands



Normal karyotyping

- * Female: 46, XX
- * Male : 46, XY

Indications of karyotyping








1. In neonate	<ul style="list-style-type: none"> - Confirm clinical diagnosis. - Dysmorphic features. - Ambiguous genitalia. - Major congenital malformations
2. In childhood	<ul style="list-style-type: none"> - Females with unexplained short stature or growth retardation. - Mental retardation of unknown origin. - Delayed puberty.
3. In adults	<ul style="list-style-type: none"> - Parents of child with chromosomal anomaly - Parents with 2 or more abortions of unknown cause. - Amniocentesis for mother with previous child with congenital anomalies and mothers > 35 years old.

Classification of Chromosomes Chromosomes are classified regarding:

- 1- Size: short, medium sized, long.
- 2- Position of centromere:
 - * Metacentric → central centromere (p arm and q arm of almost equal size)
 - * Submetacentric → (p arm shorter than q arm).
 - * Acrocentric → centromere is close to one end (very short p, very long q)

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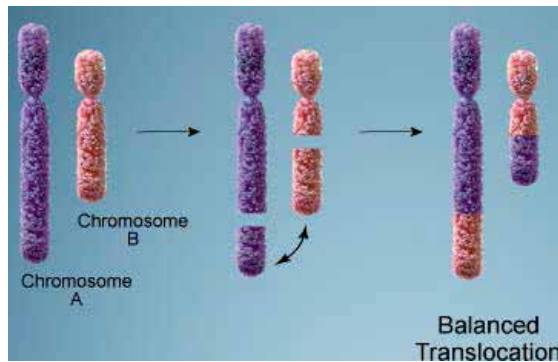
Denver classification of chromosomes: (7 groups)

A 1, 2, 3 - Large - Metacentric		B 4, 5 - Large - Submetacentric		C 6 → 12 & X - Medium - Submetacentric	
D 13, 14, 15 - Medium - Acrocentric		E 16, 17, 18 - Short - submetacentric		F 19, 20 - Short. - Metacentric	
				G 21, 22, Y - Short. - Acrocentric	

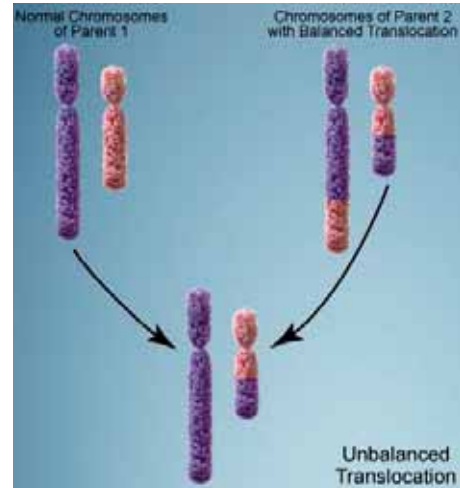
Chromosomal anomalies**A. Abnormalities of chromosome structure****1. Translocation (t)**

Part of chromosome is broken and joined to another chromosome

a. Balanced : Pieces of chromosomes are rearranged but no genetic material is gained or lost in the cell



b. Unbalanced : occurs when a child inherits a chromosome with extra or missing genetic material from a parent with a balanced translocation

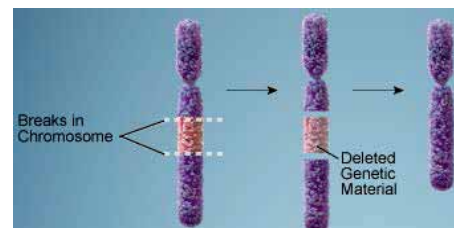
**2. Deletion (del)**

* Part of the chromosome is broken & lost \Rightarrow gene loss.

* Example:

Cri du chat syndrome (deletion chr. 5 p):

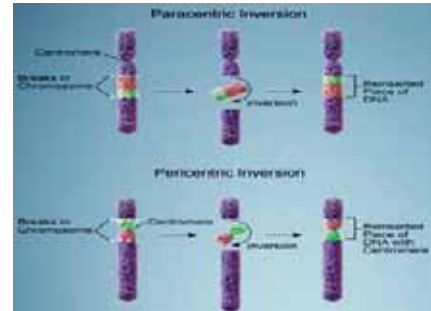
- Mental retardation & microcephaly
- Cry like cats
- Congenital heart disease



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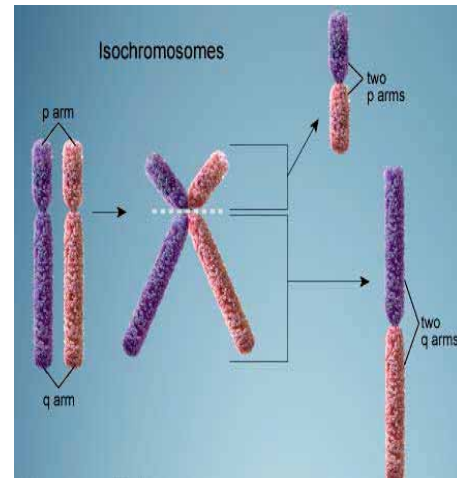
3. Isochromosome (i)

- Transverse division of the chromosome instead of longitudinal division
- Resulting in 2 chromosomes with two identical arms, either two short (p) arms or two long (q) arms



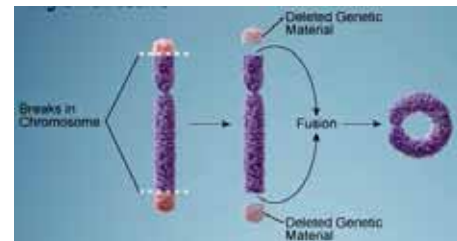
4. Inversion (inv)

- Occur when a chromosome breaks in two places and the resulting piece of DNA is reversed and re-inserted into the chromosome.
- Inversions that involve the centromere are called pericentric inversions
- Inversions that do not involve the centromere are called paracentric inversions



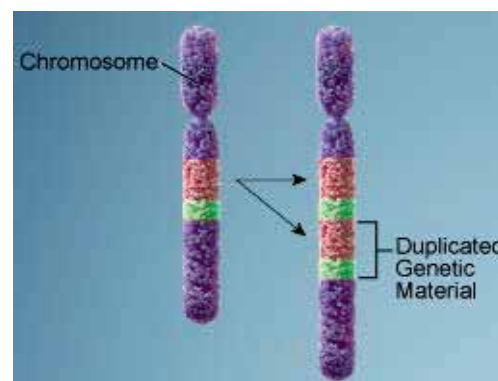
5. Ring chromosome (r)

- Breaks at both ends of a chromosome with subsequent end to end rejoining
- Often cause growth retardation and mental handicap.



6. Duplication (dup)

- * A duplication occurs when part of a chromosome is copied (duplicated) abnormally, resulting in extra genetic material from the duplicated segment



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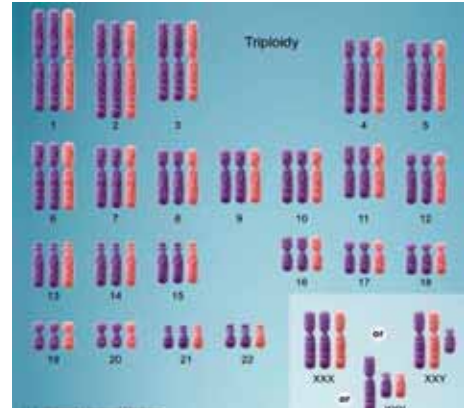
B. Abnormalities of chromosome number (Numerical anomalies)

1. **Euploidy** cells containing normal number of chromosome(23 pair)

2. **Polyploidy**

Extra whole sets of chromosomes:

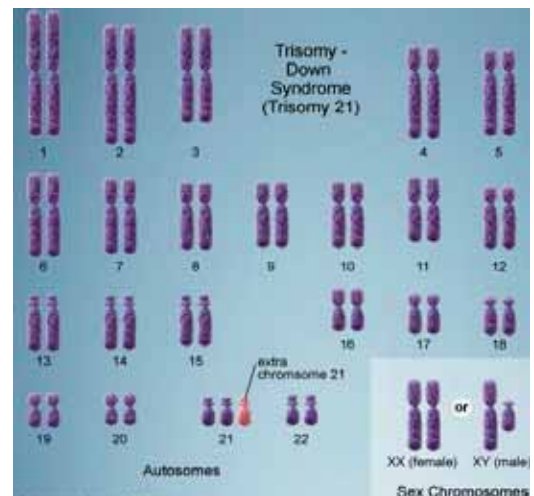
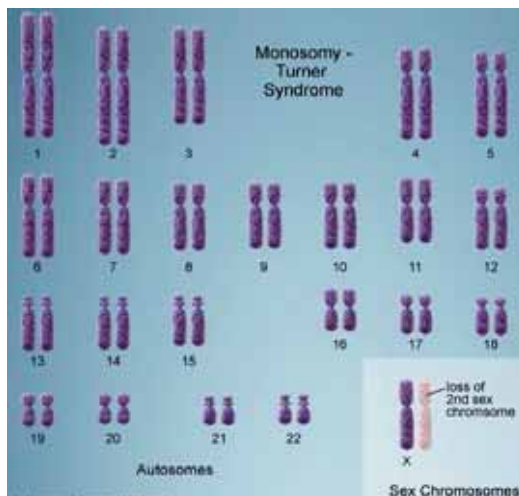
e.g. **Triploidy** 69, XXX; (lethal)



3. **Aneuploidy**: Missing or extra individual chromosomes

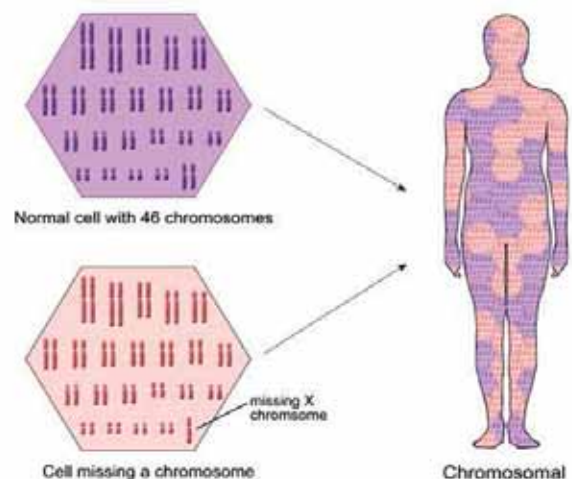
a. **Monosomy**: only one copy of a particular chromosome (most are aborted).

b. **Trisomy**: three copies of a particular chromosome



4. **Mosaicism**

- The presence of two or more different chromosome counts in different cells of the same individual
- Karyotyping of skin fibroblast help establish diagnosis as, unlike most cells, it withstand mosaicism



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Turner Syndrome

Etiology

- 1- Classic form (45, X0) \Rightarrow Monosomy X-chromosome
- 2- Deletion of short arm of one X-chromosome.
- 3- Turner mosaic: - 45 X0 / 46 X X

Clinical picture

A. At birth

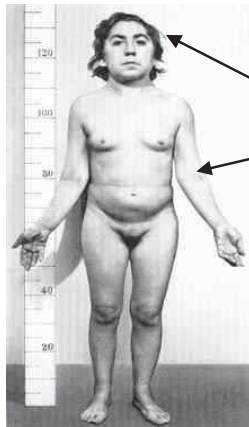


- Transient lymphoedema in dorsa of hands & feet



- Low birth weight
- Loose skin at neck nape

B. Later on



- Short female with normal mentality
- Wide carrying angle at elbow



- Low posterior hair line



- Wide spaced nipples



- Neck webbing

Diagnosis

1. For diagnosis: routine karyotyping
Karyotyping of skin fibroblast can confirm mosaic Turner

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2. For associations:

- Echocardiography: for associated congenital heart disease: Aortic coarctation
- Abdominal ultrasound: for ovarian dysgenesis (streak gonads) /Renal anomalies

Treatment

- Growth hormone
- Estrogen replacement at 14-15 years
- Specialty consultation e.g. ENT for recurrent otitis media

Klinefelter Syndrome**Etiology**

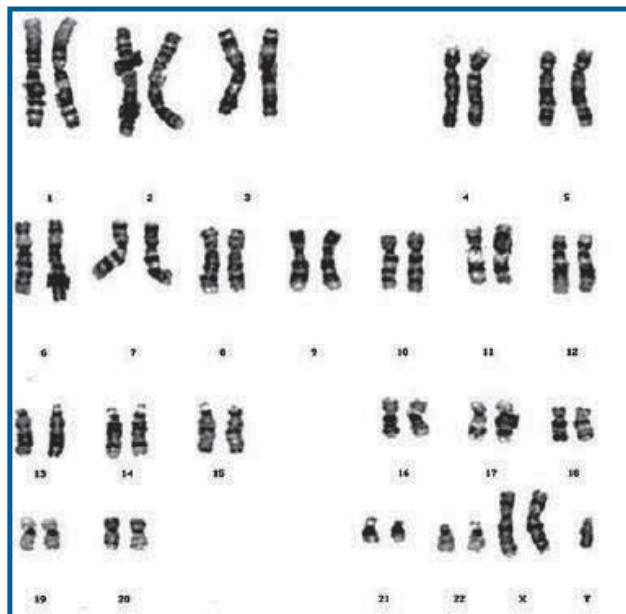
- Extra X-chromosome in a male (47, XXY) due to non disjunction.
- May be many X -chromosomes e.g. 48, XXXY,

Clinical picture

- Mental retardation
- Gynecomastia
- Diminished facial hair, feminine fat distribution.
- Atrophic testis with azospermia
- Tall stature

**Diagnosis**

1. Karyotyping: diagnostic (47, XXY)
2. Hormonal assay



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Down Syndrome

Definition: Numerical autosomal disorder (1:700 live births) Due to Trisomy 21
The extra chromosome 21 is due to

- Non disjunction occurring during gametogenesis (95% of cases)
- Translocation of an extra long arm of chromosome 21 (4% of cases)
- Mosaicism due to non disjunction occurring post fertilization (1% of cases)

Clinical picture

1. Delayed mental milestones → Mental retardation

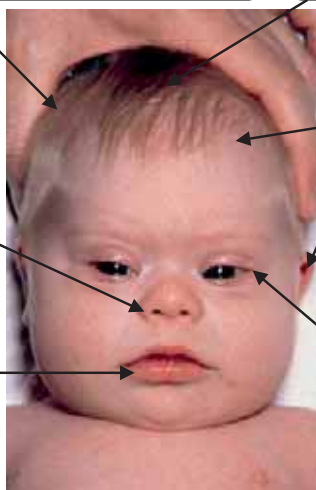
2. Delayed motor milestones: hypotonia → hyperflexible joints; Acrobat sign.

3. Head:

- | | |
|--|--|
| <ul style="list-style-type: none"> • Mild microcephaly • Brachycephaly (short anteroposteriorly) | <ul style="list-style-type: none"> • Wide posterior fontanel (at birth) • Large anterior fontanels |
|--|--|

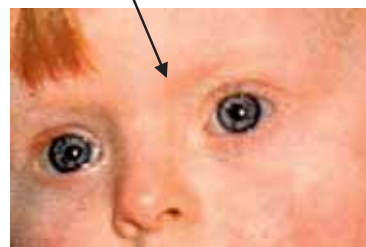
- Small nose with depressed bridge

- Small mouth
- Protruding, fissured (scrotal) tongue in a child > 6 yrs
- Delayed teething



- Fine silky hair
- Low set ears

- Hypertelorism
- Epicanthal fold
- Upward slant of eyes
- Bruchfield spots (speckled iris)



4. Heart

- Congenital heart disease in about 50% of cases
- Endocardial cushion defect and VSD

5. Abdomen

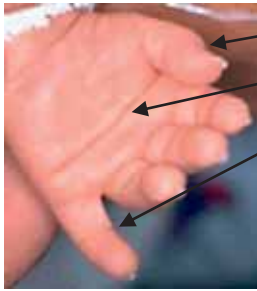
- Distended with umbilical hernia
- Visceroptosis

6. Genitalia

- Small sized (hypogonadism)
- Undescended testis is frequent

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7. Hands



- Short & broad hands
- Simian crease : one transverse crease
- Clinodactyly : incurved little finger due to rudiment middle phalanx

8. Feet



- Leading crease (Ape crease).

- Short & broad feet



- Wide gap between the first and second toes

Co morbidities/complications

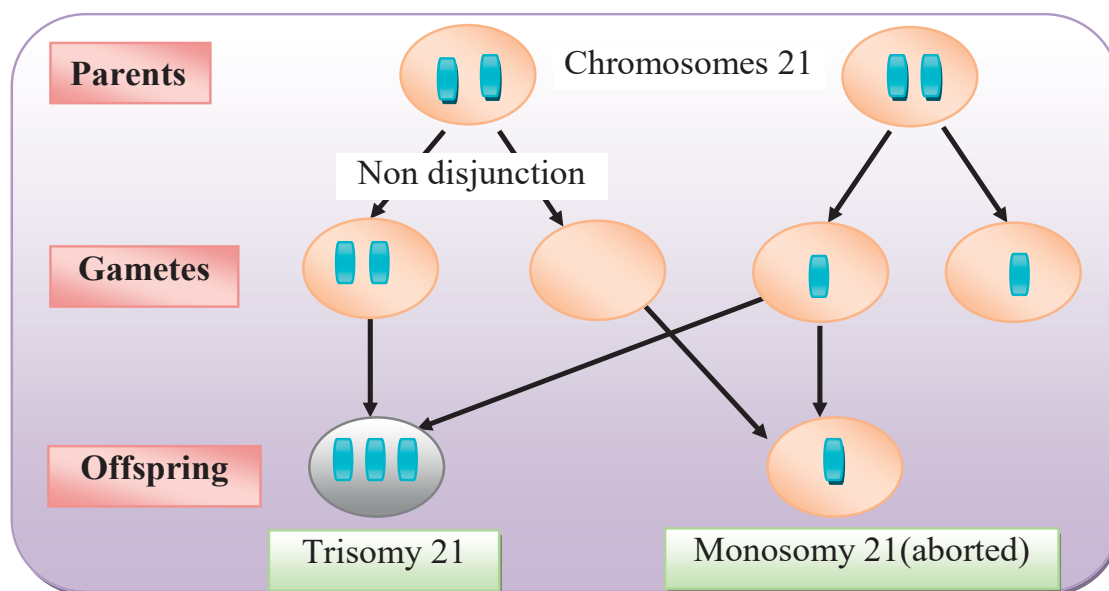
1. Immunodeficiency → recurrent infections → chest, serous otitis media
2. Neurological:
 - Mental retardation → accidental trauma
 - Atlanto axial instability with risk of spinal cord injury
 - Autism spectrum disorders, early Alzheimer
 - Strabismus, cataracts, nystagmus
3. Cardiac: Congenital heart disease → recurrent heart failure & chest infection
4. Respiratory:
 - Recurrent chest infections
 - Obstructive sleep apnea.
5. Renal anomalies.
6. Hematological: Acute leukemia (*20 times more common*).
7. Auto immune endocrinopathies
 - Hypothyroidism
 - Diabetes mellitus
 - Addison disease
8. Gastrointestinal
 - Anomalies
 - Duodenal atresia
 - Hirschsprung disease.
 - Imperforate anus
 - Celiac disease

Chromosomal Makeup of Down syndrome

Non disjunction (Regular Mongle)

Mechanism

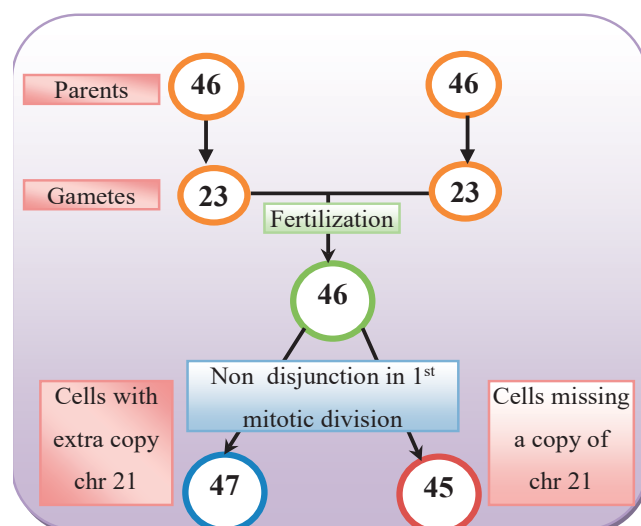
- Failure of the two chromosomes 21 to disjoin normally as it should be during gametogenesis (meiosis)→Production of gamete with an extra chromosome 21
- This extra chromosome is maternal in 97% of cases
- Recurrence rate increases with increasing maternal age (1/100 if age > 35 years)
- Baby karyotype :47 XX (+ 21) or 47 XY (+ 21); no role for parental karyotyping



Mosaic Down syndrome

Mechanism

- Non disjunction occurring post fertilization
↓
- If occurred in the 1st mitotic division→ 2 cell lines: 47, (+ 21) + 45, (- 21)
- If occurred in the 2nd mitotic division→ 3 cell lines: 47, (+ 21) + 45,(- 21) + 46
- The patient may not show all features of mongolism



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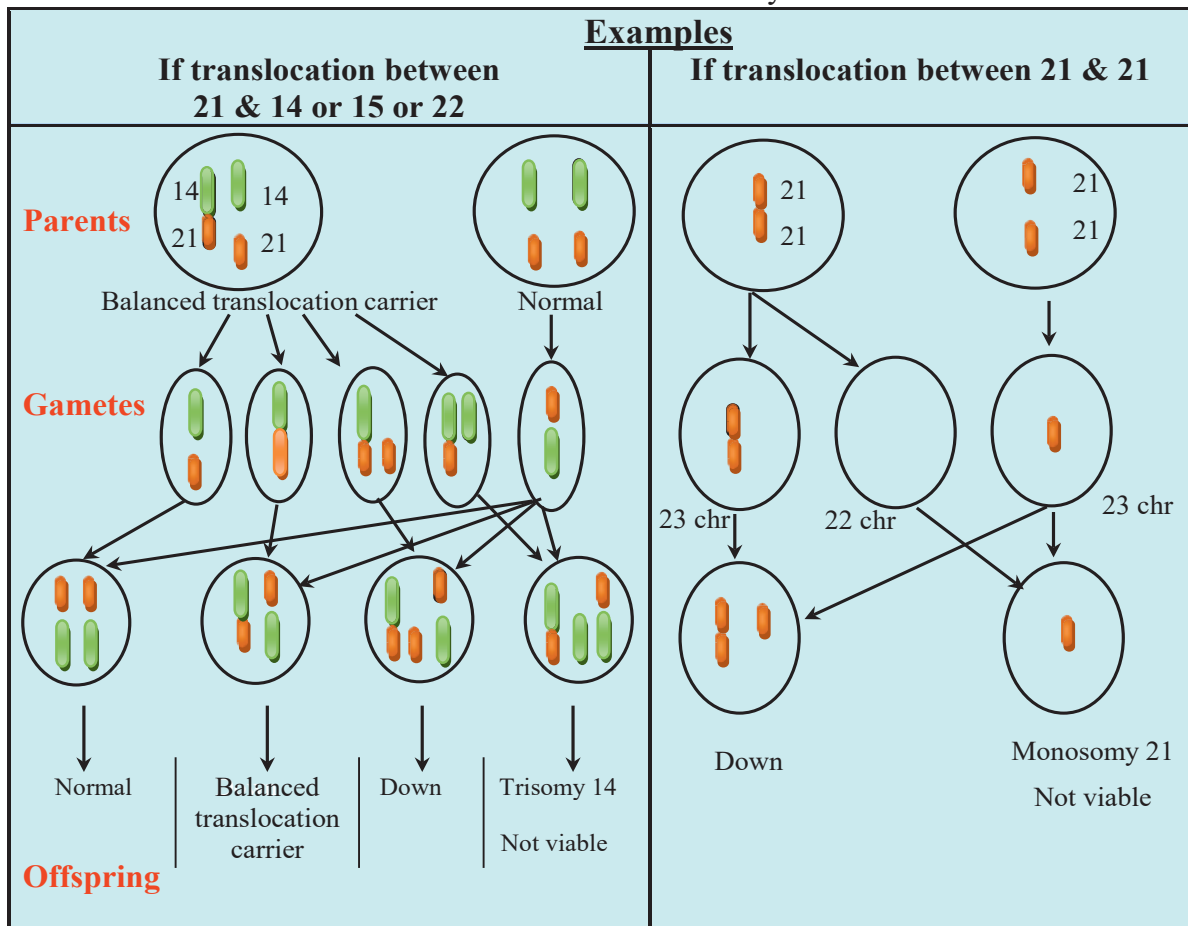
Translocation Down syndrome

Mechanism

- * Chromosome 21 is translocated onto another *acrocentric* (14, 15, 21, 22)
- * The short arms of the acrocentric chromosomes contain no essential genetic material & being very short, they are easily lost → The long arms of two acrocentric chromosomes may fuse together making one long chromosome without genetic loss.
- * If translocation occur in a parent cells → he's a balanced translocation carrier.

Recurrence rate

- ◆ Outcomes of translocation between chromosome 21 & 14, 15, or 22:
 1. Abortions
 2. Balanced translocation carrier
 3. Down syndrome
 4. Normal
- ◆ Outcomes of translocation between chromosomes 21 & 21
 1. Abortions
 2. Down syndrome



Chromosomal study

- * For baby → e.g. 46, XX, (t 21q / 14q) or 46, XY, (t 21q / 14q).
- * For parents → may show balanced translocation carrier.
e.g. Balanced translocation carrier mother : 45 ,XX ,(t 21q / 14q)

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Investigations

A- Prenatal diagnosis

1- Integrated Screening can detect up to 95% Down syndrome pregnancies using:

- Maternal age
- ↑ Fetal nuchal translucency (NT) thickness ⇒
- ↓ Pregnancy Associated Plasma Protein A
- *Quad screen* : Maternal blood shows
 - ↓ α fetoprotein
 - ↓ Unconjugated estriol
 - ↑ Free β human chorionic gonadotropin (β -hCG)
 - ↑ Inhibin



(Nelson text book)

2- Karyotyping for maternal amniotic fluid cells **or** chorionic villous sample

B. Postnatal diagnosis

1. **Clinical:** None of the clinical features is specific to Down syndrome but the associations of multiple features is usually diagnostic

2. Karyotyping

- a. For the baby to:
 - Confirm Down syndrome
 - Decide the type of Down syndrome and then the risk of recurrence
- b. For the parents if the baby translocation type


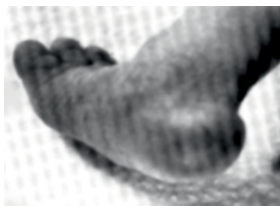



Health supervision of Down syndrome

- Multidisciplinary care approach is the mainstay for management
- Screen for and manage complications

Condition	Time to screen
• Congenital heart disease	- At birth and young adult for acquired valve disease
• Strabismus, cataracts, nystagmus	- Birth or by 6 mo; by pediatric ophthalmologist - Check vision annually
• Hearing impairment or loss	- Birth or by 3 mo with auditory brainstem response or otoacoustic emission testing - Check hearing q6mo -1 year
• Celiac disease	- At 2 years or with symptoms(IgA and tissue transglutaminase antibodies)
• Hypothyroidism	- Birth; repeat at 6-12 mo and annually
• Obstructive sleep apnea	- Start at 1 yr and at each visit - Monitor for snoring, restless sleep
• Atlantoaxial subluxation or instability (incidence 10-30%)	- Radiographs at 3-5 years or when planning to participate in contact sports, diving, swimming - Radiographs indicated wherever neurologic symptoms are present even if transient (neck pain, torticollis, gait disturbances, weakness)

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Other Trisomies

	Trisomy 18 (Edward's Syndrome)	Trisomy 13 (Patau syndrome)
Incidence	1/7000 live births	1/10.000
Karyotyping	47, +18	47, +13
<u>Clinical picture</u> a. Common features: <ul style="list-style-type: none"> - Growth retardation - Microcephaly and Mental retardation - Dysmorphic face - Congenital heart diseases (VSD, PDA , ASD) - Visceral anomalies - Most die in the 1st year of life b. Specific features:		
	<p>* Prominent occiput.</p>  <p>* Hypertonia with Closed fist and overlapping fingers</p>  <p>* Rocker bottom heel</p>	 <p>* Scalp defects(cutis aplasia) * Brain malformations</p>  <p>* Cleft lip and palate</p>  <p>* Polydactyly</p>

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Self-Assessment Case Scenarios

Case 1

15 years old girl presented to outpatient clinic for routine check ;she have not got menses yet, her height was 125 cm(< 3 rd percentile), no physical signs of puberty, with unusual facial appearance unlike her parents and her siblings; cardiac auscultation showed ejection systolic murmur over left sternal border. She is doing well in school and thyroid profile is normal.

- a. Suggest a diagnosis?
- b. How can you confirm diagnosis?

Case 2

A two day old male infant is referred from a community hospital for bilious vomiting and a heart murmur. The baby was born at 37 weeks gestation to a 39 year old woman who had no prenatal care. Exam: vital signs Temp 37.1 (ax), Pulse 150, Respiratory rate 45, BP 75/50, oxygen saturation 99% in room air. Height, weight and head circumference are at the 50th percentile. He appears jaundiced, and has a flat facial profile; short, upslanting palpebral fissures; a flat nasal bridge with epicanthal folds; a small mouth with protruding tongue; and single palmar creases. His lungs are clear to auscultation. His heart is tachycardic with a loud holosystolic murmur. His abdomen is non-distended. Generalized hypotonia is present. An abdominal radiograph shows a "double-bubble sign".

- a. What is the most likely clinical syndrome?
- b. What are the current co morbidities?
- c. What are immediate lines of treatment?
- d. Other workup?

Case 3

A 7-year-old patient who has Down syndrome is brought to the clinic by her mother, who is worried that the child has an increasingly abnormal gait and worsening clumsiness. On physical examination today, you note that she has an unsteady gait, and she has brisk deep tendon reflexes diffusely. These findings represent a significant change from 9 months ago when your neurologic examination showed only slightly diminished tone.

What the most likely cause of these symptoms and signs?

Case 4

A 7-year-old patient who has Down syndrome is brought to the clinic by her mother, who is worried that the child has an increasing pallor ,lethargy and abdominal distension. Examination revealed few purpuric spots, bilateral axillary and cervical lymph nodes enlargement and significant hepatosplenomegaly

What is the likely diagnosis? Two investigations required?

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الدفعۃ ال14

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الدفعۃ ال14



Diarrheal disorders

Diarrheal Disorders

Definition of diarrhea

* WHO defines diarrhea as: the increase of volume, fluidity, or frequency of motions relative to the usual pattern of the individual

Classification of diarrhea

- i. **Acute Diarrhea** : - Starts acutely
- Watery without visible blood
- Last less than 14 days.
(**Dysentery** is acute diarrhea with visible blood in stool)
- ii. **Persistent diarrhea**: Started as acute diarrhea (watery **or** dysentery) but persists more than 14 days
- iii. **Chronic diarrhea**: - Diarrhea of gradual onset, lasting ≥ 1 month **or** recurrent due to non infectious cause

Mechanisms of Diarrhea

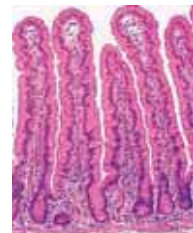
A. Enteric infection

1. Type I: Non-inflammatory

- Due to
 - a. **Superficial mucosal invasion** due to:
 - Viral e.g. Rota virus
 - Bacterial e.g. Enteroinvasive E. coli, Campylobacter
 - b. **Mucosal adhesion** by e.g. Enteropathogenic E. coli, Giardia lamblia

Mechanism

Superficial invasion or adherence of the absorptive villi cells with intact secretory crypt cells → crypt cells continue secretions with impaired villi cells absorption



c. **Entero toxin production**

Example: Enterotoxigenic E coli, and vibrio Cholera

Mechanism

Enterotoxin stimulates adenylate cyclase enzyme in crypt cells → excessive cyclic AMP production → excessive intestinal secretions

- Location of enteric infection: Proximal small bowel
- Illness : Watery diarrhea (**Secretory diarrhea**)
- Stool exam : No fecal leukocytes

2. Type II: Inflammatory

- Due to: Mucosal invasion and cytotoxin production
- Illness :Dysentery
- Location: Colon
- Stool exam : Fecal neutrophils and ↑↑ Lactoferrin



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3. Type III: Penetrating

- Due to: Penetration by Salmonella typhi and para typhi, Yersinia enterocolitica
- Illness : Enteric fever
- Location: Distal small bowel
- Stool exam : Fecal mononuclear leukocytes

(Nelson text book of pediatrics, 2016)

B. Osmotic diarrhea

Intestinal villi damage leads to loss of disaccharidases (e.g. lactase) → accumulation of non-absorbable solutes in intestinal lumen → osmotic load → shift of water to the intestinal lumen → diarrhea

Differences between secretory and osmotic diarrhea

	Secretory diarrhea	Osmotic diarrhea
Volume	Large	Small
Effect of fasting	Diarrhea continues	Diarrhea stop
Food type	Unrelated	Usually related.
<u>Stool analysis</u>		
- Stool pH	Alkaline	Acidic
- Reducing substance	Absent	May be present
- Fecal sodium& chloride	High	Low

Acute non infectious diarrhea

1. Dietitic

- Over feeding
- Under feeding: Starvation diarrhea (scanty, greenish, ↑mucus)
- Bad feeding:
 - Change in formula type or concentration
 - Introduction of new unsuitable food.
- Lienteric diarrhea: Hyperactive gastro-colic reflex → motion short after every feed



2. Drugs

- Prolonged oral antibiotics (e.g. ampicillin)
- Laxatives to the baby or to lactating mother.



3. Parental diarrhea (2nd gastro enteritis).

- Due to infections outside GIT e.g. otitis media, respiratory infections.
- Possible mechanisms; toxic absorption or reflex gastro intestinal irritation
- The term parenteral diarrhea is no longer used due to possible intestinal infection.

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Acute infectious diarrhea (Gastro Enteritis)

Gastroenteritis is due to infection acquired through the fecal-oral route or by ingestion of contaminated food or water

Severity

- * Mild = 4-6 motions /day
- * Moderate = 6-10 motions /day
- * Severe > 10 motions /day

Causes of Gastroenteritis

1. Viral (60%)

Examples

- Rota virus.
- Norwalk like viruses
- Adenovirus

Clinical features

- Age usually less than 2 years.
- Common in winter
- May be associated upper respiratory tract infections
- Pyrexia if present usually (< 38.5 °C).
- Diarrhea is:
 - Mild to moderate.
 - Transient = (5-7 days)
 - Watery
 - Odorless

2. Bacterial

Clinical features

- Common in summer
- With high fever (>38.5 °C)
- Cramping abdominal pain
- Usually severe diarrhea which may be:-
- * Bloody with:
 - Salmonella
 - Shigella desentyrice type 1.
 - Entero invasive E-Coli.
 - Entero hemorrhagic (*Shiga toxin producing*) E-Coli
- * Watery
 - Shigella (diarrheal type)
 - Entero pathogenic E-Coli
 - Entero toxigenic E-Coli
 - Vibrio cholerae O1.
- * Watery offensive for 2-4 days then turn bloody → Campylobacter jejuni.

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3. Protozoal

- **Giardia Lambelia**
 - Watery
 - Offensive
 - No fever
- **Entameaba histolytica**
 - Bloody, may be with tenesmus
 - No fever usually

Complications of Gastroenteritis

1. Dehydration

- Fluid loss due to vomiting, diarrhea and anorexia (see later)
- The main cause of death in gastroenteritis

2. Shock

Types

- Hypovolemic shock with severe dehydration
- Gram negative septic shock.

Clinically

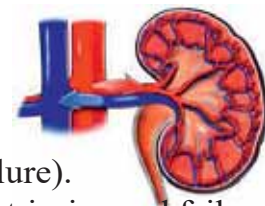
- Decreased peripheral perfusion
 - Skin mottling , capillary refill time >2 seconds→
 - Cold extremities
- Decreased vital organs perfusion
 - Brain → lethargy
 - Kidney → oliguria
- Hypotension and rapid thready pulse



3. Acute renal failure (ARF)

Due to

- Hypovolemia → ↓ renal blood flow (pre renal failure).
- Untreated pre renal failure → tubular necrosis → intrinsic renal failure



Clinically

- Oliguria or anuria
- Acidotic breathing (Rapid, deep breathing).

4. Metabolic Acidosis

Due to

- Loss of bicarbonate in the stool
- Acute renal failure

Clinically

- Acidotic breathing (rapid deep breathing pattern)
- Disturbed consciousness.
- Arterial blood gases (↓pH, ↓PaCO₂, ↓HCO₃)



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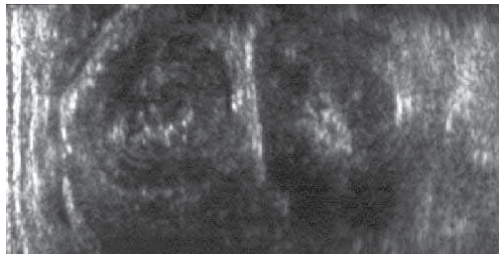
5. Electrolyte disturbance

- Hypokalemia: (serum potassium < 3 meq /L)
Clinically
 - Apathy (disturbed consciousness)
 - Arrhythmias
 - Abdominal distension (paralytic ileus)
 - Atony (Hypotonia).
- Hypocalcemia: → Tetany or Convulsions
- Hypo or hyper natremia: → Convulsions

6. Convulsions → possible causes:

- Hypoglycemia ; mainly in mal nourished.
- Hypo or Hypernatremia.
- Hypocalcemia
- CNS infections e.g. meningitis or encephalitis may due to shigella or neurotropic virus

7. Bleeding

Possible causes	Clinically
<u>DIC</u> due to shock, sepsis <u>or</u> acidosis	- Bleeding tendency ;initially from puncture - Skin gangrene
<u>Intussusception</u> Part of the intestine invaginates in the distal part 	- Attacks of abdominal <u>pain</u> (screaming) - Vomiting with constipation - <i>Redcurrant</i> jelly stool - Sausage shaped abdominal mass - P/R → head of intussusception may be felt - Ultrasonography is diagnostic & safe - Air contrast enema → can be therapeutic 
<u>Renal vein thrombosis</u> due to severe dehydration → hypovolemia → venous stasis	- Hematuria - Flank (Renal) mass - If bilateral → acute renal failure

8. Persistant diarrhea and eventual Malnutrition

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Workup of Gastroenteritis

1. For the cause

- Stool analysis for blood, fecal leucocytes , Rotazyme test, parasites
- Stool culture

2. For the complications (more important)

- Routine: Blood urea nitrogen, creatinine, sodium ,potassium, and calcium.
- Blood gases → for metabolic acidosis.
- Coagulation profile → PT, PTT, FDPs, platelets for bleeding
- Others: According to clinical suspicion e.g. Abdominal ultrasound /X ray

Treatment of Gastroenteritis

- **GE with no or minimal dehydration (plan A):** Home management

1. Fluid therapy

Avoid dehydration by plenty of fluid:

- Use oral rehydration solution (ORS).
- Amount of ORS:

Weight	ORS amount after each loose motion or vomiting episode
< 10 kg	60-120 ml
> 10 kg	120-240 ml

- Food based fluids for infants > 6months or weaned:
 - Rice water, soup, and yogurt drinks
 - Avoid hyperosmolar fluids as it increases the diarrhea

2. Feeding to avoid malnutrition

- Continue breast feeding or usual milk formula
- For infants > 6months, give: mashed potatoes, cereals, and BART (Banana, Apple juice, Rice, Toast)

3. Follow up and medical advice if

- No improvement for 3-5 days
- Presence of a warning sign: (*Reminder: Bloody FEVER*)
 - **Bloody** motions.
 - High **Fever**.
 - Eager to drink (Marked thirst)
 - Frequent Vomiting.
 - Excessive watery motions
 - Refusal of oral fluids or feeding.



- **GE with dehydration (plan B & C) ⇒ See dehydration**
- **Antibiotics**

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- * **Indications** : - If bacterial cause is identified or strongly suspected.
 - Associated bacterial infection (e.g. otitis media)
 - (Fever per se is not an indication for antimicrobial therapy)
- **Anti-parasitic**
 - * *Entamoeba histolytica* : Metronidazole **50 mg/kg /day** for **10 days** oral.
 - * *Giardia lamblia* : Metronidazole **15 mg/kg** for **7 days**.
- **Treatment of complications e.g.**
 - Acute renal failure → Usually pre renal responds to rehydration / consult pediatric nephrologist in unresponsive cases
 - Hypocalcemia → Calcium gluconate 10% slow i.v.
 - Hypokalemia → Add potassium to the IV fluids
 - Convulsions: - Anticonvulsants (e.g. Diazepam) and treat the cause.
- **Additional therapy:**
 - Probiotics : non pathogenic bacteria e.g. *lactobacillus* .
 - Oral Zinc 10 - 20mg /day
- **Prevention of gastroenteritis**
 - Promote exclusive breast feeding for the first 6 months and continued during illness including diarrhea
 - Proper weaning
 - Rota virus (Rotarix)vaccines
 - Hygienic measures

Dysentery

Acute diarrhea with visible blood in the stool

Causes

- 1- *Shigella* Desentyrie (commonest cause).
- 2- Enteroinvasive *E.coli* and Entero hemorrhagic *E- coli* (O157:H7)
- 3- *Campylobacter jejuni*.
- 4- *Salmonella* (rare).
- 5-*Entamoeba histolytica* (uncommon before 5 years old)

Clinical picture

- 1- Acute **bloody** diarrhea with mucus & pus
- 2- Severe crampy abdominal **pain**
- 3- Tenesmus (painful defecation)
- 4- **Pyrexia** / dehydration/ toxic manifestations

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Complications

1. As for acute diarrhea
2. Hemolytic uremic syndrome ; associated with *Shiga toxin* (or *Verotoxin* producing entero hemorrhagic E- coli and Shigella

Differential diagnosis

1. Intestinal obstruction e.g. Inussuption and volvulus
2. Ulcerative colitis

Investigations

- Stool analysis
- Stool culture
- CBC and blood urea and electrolytes

Treatment

- * Supportive : As for acute diarrhea ; Fluid therapy , Feeding , Follow up
- * Treat complications
- * Treat the cause

Persistent Diarrhea (post gastro enteritis syndrome)

Definition

- Acute diarrhea (watery **or** dysentery) which persists **more** than 14 days
- About 10% of acute diarrhea progress to persistent diarrhea
- Persistent diarrhea carries high risk of malnutrition and high mortality

Etiology

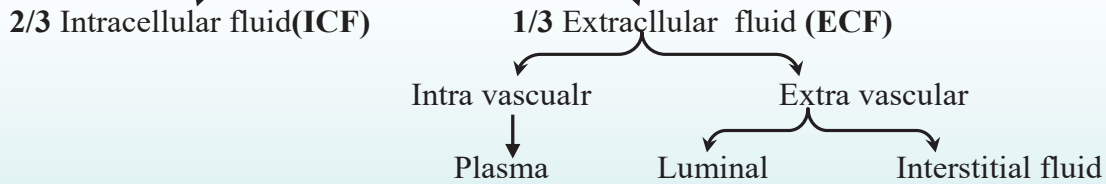
1. Persistent infection e.g. Giardia lamblia, salmonella
2. Post-enteritis malabsorption:
Damaged villi cells with 2^{ry} dissacharidase deficiency:
 - Lactase deficiency→ Lactose intolerance (diarrhea which increases with lactose containing milks)
 - Invertase deficiency →Sucrose intolerance (diarrhea which increases with sucrose containing milks)

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Dehydration

Introduction

Body water is distributed as



Intracellular electrolytes		Extracellular electrolytes in meq/l	
Main cation	Main anions	Cations	Anions
Potassium (K)	Phosphate Proteinate	Na 135-145 K 3.5-5 Ca 9-11 (mg/dl) Mg 1.5 – 2.5	CL 105 HCO ₃ 26

Q Infants are more susceptible to dehydration than adults, why?

- Higher total body water; 75% of body weight in contrast to 60 % in adults .
- Higher daily requirements of water in (150 ml /kg/d)
- Higher frequency of diarrheal diseases

Definition

Dehydration means loss of water & electrolytes from ECF ; The ICF may be secondarily affected.

Etiology

1. Diarrheal diseases
2. Others : - Decreased intake e.g. starvation, coma , poor hydration in illnesses
 - Vomiting e.g. Congenital pyloric stenosis, intestinal obstruction.
 - Hyperventilation.
 - Burn
 - Fevers and hyperprexia
 - Excessive sweating
 - Polyuria e.g. diabetes mellitus, diabetes insipidus, chronic renal failure, hypercalcemia , diuretics overuse

Degrees of dehydration

1. According to degree of body weight loss (Relative to pre illness weight)

Dehydration	Body weight loss	Clinically
Minimal or absent	< 3%	Few or absent signs of dehydration
Mild to Moderate	4-9%	Typical picture of dehydration
Severe	≥ 10%	Hypovolemic shock

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2. According to WHO guidelines

	Plan A	Plan B	Plan C
Definition	No dehydration	Mild to moderate dehydration.	Severe dehydration
General appearance	Normal, alert No shock	Irritable, restless No shock	Shocked →hypotension, ↑ pulse → lethargy, oliguria → cold mottled skin.
Eyes → look → tears	Normal Present	Slightly sunken Decreased	Deeply sunken. Absent
Mouth → tongue → thirst	Moist Absent	Dry <i>Drinks eagerly</i>	Very dry (parched) <i>Unable to drink.</i>
Skin pinch (Turgor)	Normal Instant recoil	<i>Goes back slowly</i> Recoil in <2 sec	<i>Goes back very slowly</i> Recoil in >2 sec
Fontanel	Normal	Depressed	Depressed

N.B : - Key signs of dehydration include: general appearance, thirst, & poor skin pinch.
- 2 or more signs including at least 1 key sign should exist to assign certain plan

Types of dehydration

Hypotonic(Hyponatremic).	Isotonic(Isonatremic)	Hypertonic(Hypernatremic)
Serum Na < 130 meq/ L	130 - 150 meq/ L	> 150 meq/ L
A/E: Excessive intake of water or hypotonic fluids during diarrhea → loss of electrolytes > loss of water → Overhydrated cells → Marked collapse of ECF	Equal loss of water and electrolytes leading to:- → Normal cellular hydration → Collapsed ECF	Excessive intake of hypertonic fluids during diarrhea → poor absorption → ↑ osmosis → loss of water > electrolytes loss → Dehydrated cells → Normal ECF

Clinical features

Manifestations of ICF affection

Tongue: - Moist	- Dry; thirsty	- Very dry (woody); marked thirst
Brain: - Lethargy - Coma - Convulsions	- Irritable	- Irritable - Hyper-reflexia - Convulsions

Manifestations of ECF affection

Shock - Rapidly occurring	- Slowly occurring	- Usually absent
Skin turgor - Marked loss	- Moderate loss	- Normal (or doughy)
Fontanels - Markedly depressed	- Moderately depressed	- Normal or bulging
Eyes - Markedly sunken	- Moderately	- Mildly sunken

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Complications of dehydration

Complications of gastro enteritis plus

- **Hemoconcentration** → phlebothrombosis especially in cortical & renal veins.
- **Hypokalemia** → aggravated by rapid correction of acidosis → intracellular shift of potassium
- **Hyperkalemia** :
 - Aggravated by: Acidosis and excessive potassium infusion in presence of renal impairment.
 - Manifested by: - Restlessness
 - Cardiac arrhythmias (bradycardia, cardiac arrest)

(N.B: Potassium disorders are readily detectable by ECG)

- **Hypernatremic dehydration hazards:**

1. Seizures may be due to:

- * Intracranial hemorrhage: Brain cells dehydration → ↓ brain volume → tear of intracerebral & bridging blood vessels.
- * Rapid lowering of serum Na → brain cells overhydration → brain edema.
- * Associated Hypocalcemia is common.

2. Renal tubular injury → acute renal failure

Treatment of dehydration

I. Mild to moderate dehydration (Plan B dehydration)

① Deficit therapy

- Fluid type ? → Oral rehydration solution (ORS)
- Amount ? → **50-100 ml/kg** over **4 hours** (if child wants more, give more)
- Route ? → One tea spoonful/1-2 minutes orally

Problems during deficit therapy

Problem	Management
• Vomiting	* Wait 10 minutes * ORS is given at slower rate (spoon / 2-3 minutes)
• Refusal of ORS • Frequent vomiting	* ORS can be given more slow by nasogastric tube
• Coma • Persistent vomiting • Abdominal distension • Paralytic ileus. • Rapid loss of stool	* Deficit therapy is given parenterally (IV) • Amount of fluid: 50-100 ml/kg • Type of fluid: – Poly electrolyte solution (Polyvalent) or – Glucose: Saline mixtures : 5% dextrose in ½ Normal saline

(Nelson text book of pediatrics)

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② Feeding

- * Breast fed → continue
- * Non breast fed → give usual formula after the first 4 hours
- * If child > 6 months or weaned → give plenty of fluid and food as in plan A.

③ Assessment after deficit

• Good response

- * Criteria:
 - No signs of dehydration
 - Baby fall asleep
 - Pass urine
- * Decision: Continue replacement as for plan A (see before)

• Still dehydrated → Repeat the deficit therapy

• Worsening (Severe dehydration) → Treat as plan C

II . Severe dehydration (Plan C dehydration)

① Shock therapy

- Fluid type ? → lactated Ringer (**or** physiological saline).
- Amount ? → **20** ml/kg over ½- 1 hour
- Route ? → Parenteral(intravenous or intraosseus)

After shock therapy

• Good response

- ⊕ Criteria:
 - Improved mental state
 - Improved perfusion
 - Able to drink
- ⊕ Decision: Treat as for mild to moderate dehydration (**R/ Deficit Therapy**)
Give **100** ml/kg of previous fluids over 4 hours

• Still shocked

- ⊕ Criteria: Lethargic, weak pulse, poor capillary refill
- ⊕ Decision: - Repeat shock therapy.

② Assessment

After 6 hours in infants < 1 year and after 3 hours in older child

Finding	Decision
Severe dehydration	- Restart rehydration therapy as for plan C - Think of and treat complications
Mild to moderate dehydration	- Continue as plan B
No signs of dehydration	- Continue as plan A

③ Feeding ⇒ As in plan B

Don't forget: Specific treatment (e.g. Antibiotics) and treat complications

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Precautions during hypernatremic dehydration treatment

- Type of fluid: Glucose 5% in $\frac{1}{2}$ normal saline
- Under correction → water deficit should be replaced over more than 36 hours
- Slow correction → Reduce serum Na by no more than 0.5 mEq/L per hour
- Monitor serum Na & Ca closely during treatment.
- If convulsions occur during treatment → treat the cause:
 - * Rapid lowering of Na → NaCl 3% 2-4 ml/kg very slow i.v
 - * Hypocalcemia → Ca gluconate 10% 1-2 ml/kg very slow i.v
 - * Brain edema (due to rapid or over hydration) → mannitol 20% over 20min.

(See Prevention and treatment of viral gastroenteritis in children, UpToDate)

Oral rehydration solution (ORS)

- * **Mechanism of ORS** → co absorption of Na & glucose or certain amino acids even via damaged intestinal mucosa → other electrolytes esp. Chloride are absorbed 2^{ry} to Na.

1. **Standard ORS**(Rehydran sachets)

- Rehydran sachets: each sachet contain:-
 - Sodium chloride 0.7 Gram
 - Sodium citrate 0.5 Gram
 - Potassium chloride 0.3 Gram
 - Glucose 4 Gram

Each sachet is dissolved in **200 ml** clean water

- WHO ORS → Contains same ratios as Rehydran ; dissolved in **1 liter**

2. **Other types of ORS:**

- Lohydran → With lower sodium chloride content
- ReSoMal: - ORS containing less Na , more K with added magnesium & zinc.
- Mainly for rehydration of severely malnourished infants.

<u>Advantage of ORS</u>	<u>Limitations of ORS</u>
<u>Fit for</u> <ul style="list-style-type: none"> • All types of dehydration • Any age even the newborn • Any type of diarrhea 	<u>Not fit for</u> <ul style="list-style-type: none"> • Shocked cases (unable to drink) • If intra venous fluids are indicated • Glucose malabsorption (rare)

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Malabsorption Syndrome

Definition

- Diminished intestinal absorption of one or more dietary nutrients
- Due to either defective nutrient digestion or mucosal absorption
- Steatorrhea → with fat malabsorption = pale, bulky, greasy, offensive stool

Etiology

1- Impaired digestion

- * Hepatic
 - Biliary atresia (bile salt insufficiency)
 - Chronic hepatitis
- * Pancreatic:
 - Prolonged protein calorie malnutrition
 - Cystic fibrosis
 - Chronic pancreatitis
 - Shwachman-Diamond syndrome

2- Intestinal stasis

- Protein caloric malnutrition (acini atrophy).
- Stagnant loop syndrome.
- Inflammatory bowel diseases:
 - Crohns' disease
 - Ulcerative colitis

3- Impaired absorption

a. Generalized malabsorption:

- Chronic infections: e.g. giardia lamblia, tuberculous enteritis , bilharziasis
- Congenital: chloride diarrhea, sodium diarrhea
- Defective enterocyte differentiation: microvillous inclusion disease, congenital tufting enteropathy
- Short bowel syndrome
- Celiac disease
- Auto immune enteropathy
- Allergy: Multiple food protein hypersensitivity
- Intestinal tumors

b. Specific malabsorption:

Type	Example
Specific carbohydrate malabsorption	<ul style="list-style-type: none"> - Lactose malabsorption - Glucose galactose malabsorption - Fructose intolerance
Specific fat malabsorption	<ul style="list-style-type: none"> - Abetalipoproteinemia
Specific amino acids malabsorption	<ul style="list-style-type: none"> - Enterokinase enzyme deficiency - Hartnup disease(neutral amino acids) - Blue diaper syndrome(tryptophan)

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Type	Example
Specific vitamin malabsorption	- Vitamin D , folic acid , B ₁₂
Specific mineral malabsorption	- Acrodermatitis enteropathica(zinc) - Menkes disease (copper)

Clinical picture

- 1- Features suggesting a cause e.g.- Hepatomegaly & jaundice in chronic liver disease.
- Relation to certain food in celiac disease.
- 2- General ill health with pallor, weakness & failure to thrive
- 3- Gastrointestinal manifestations of malabsorption
 - Mouth ulcers & glossitis
 - Abdominal distension & flatulence
 - Steatorrhea : pale, bulky, greasy, offensive stool
 - Chronic diarrhea
- 4- Nutritional deficiency manifestations
 - Fat : Loss of subcutaneous fat
 - Proteins: Nutritional edema , muscle wasting & loss of weight
 - Carbohydrates : Hypoglycemia
 - Minerals and vitamin deficiency

N.B: Acrodermatitis enteropathica (autosomal recessive Zinc malabsorption);

- Dermatitis → peri facial and peri anal & extremities
- Alopecia.
- Chronic diarrhea→ protein losing enteropathy



Investigations

A- Stool examination to prove malabsorption

- * For carbohydrate malabsorption:
 - Stool pH (may be acidic)
 - Reducing substances in stool.
 - Breath hydrogen test.
- * For fat malabsorption:
 - ↑ Stool fat globules.
 - ↑ Stool fat content (Steatocrit test).
- * For protein malabsorption.
 - ↑ Fecal α_1 antitrypsin.

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B- For the cause:**STEP 1**

- Intestinal Microbiology
 - Stool cultures
 - Microscopy for parasites
 - Viruses
 - Breath hydrogen test
- Screening Test for Celiac Disease
- Sweat chloride test for cystic fibrosis.
- Noninvasive Tests for:
 - Intestinal function e.g. iron absorption test
 - Pancreatic function (amylase, lipase, fecal elastase)
 - Intestinal inflammation (fecal calprotectin, rectal nitric oxide)
- Tests for Food Allergy: Prick/patch tests for foods
- Abdominal Ultrasounds (Scan of Last Ileal Loop)

STEP 2

- Evaluation of Intestinal Morphology:
 - Endoscopy and jejunal/colonic histology /Electron microscopy
 - Imaging (upper or lower bowel series, capsule endoscopy and the new SmartPill measures pressure, pH, and temperature)

STEP 3: Special Investigations:

- Intestinal immunohistochemistry
- Anti-enterocyte antibodies
- Serum catecholamines
- Autoantibodies
- Brush-border enzymatic activities
- Motility and electrophysiologic studies

(Nelson textbook of pediatrics)

Treatment

- 1- Treat the cause (medical or surgical)
- 2- Adequate nutrition
 - Avoid causative food
 - Medium chain triglycerides
 - Supplemental minerals & vitamins.

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Celiac disease

Definition

- An immune-mediated (T-cell) systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals
- Triggered by the ingestion of wheat gluten (contains epitopes from gliadin which are highly resistant to intraluminal and mucosal digestion) and related prolamines from rye and barley → incomplete degradation favor the immunostimulatory and toxic effects → severe intestinal mucosal damage (**Gluten Sensitive Entropathy**).
- Frequent associations
 - Type 1 diabetes, autoimmune thyroid disease, Addison disease, selective IgA deficiency, intestinal lymphoma and rheumatoid arthritis
 - Down, Turner, and Williams syndromes

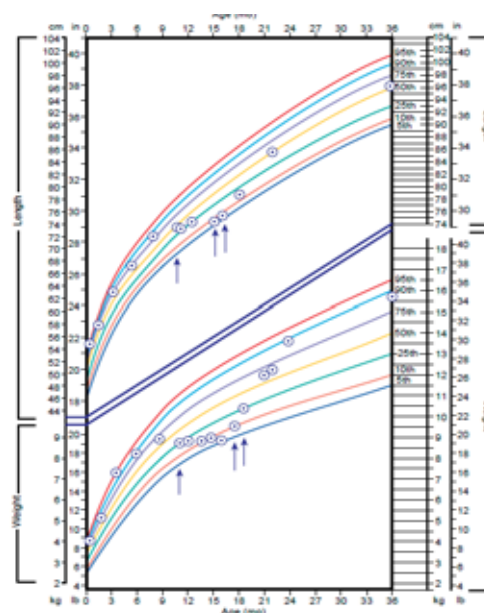
Clinical spectrum

Symptomatic:

1. Frank malabsorption
 - Chronic diarrhea (steatorrhea) with large pale, bulky, greasy, offensive stool
 - Present around 6th – 12th month with feeding gluten diets
 - Abdominal distension & pain → irritability
 - Features of malabsorption syndrome (*see before*)
 - Failure to thrive due to steatorrhea & marked anorexia
 - Finger clubbing
2. Extra intestinal manifestations:
 - Iron-deficiency anemia, unresponsive to iron therapy (most common)
 - Short stature
 - Arthritis and arthralgia
 - Aphthous stomatitis
 - Peripheral neuropathies
 - Cardiomyopathy
 - Isolated hypertransaminasemia

Growth curve demonstrates initial normal growth from 0-9 mo, followed by onset of poor appetite with intermittent vomiting and diarrhea after initiation of gluten-containing diet (*single arrow*). After biopsy confirmed diagnosis and treatment with gluten-free diet (*double arrow*), growth improves

(Nelson 2016)



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Silent

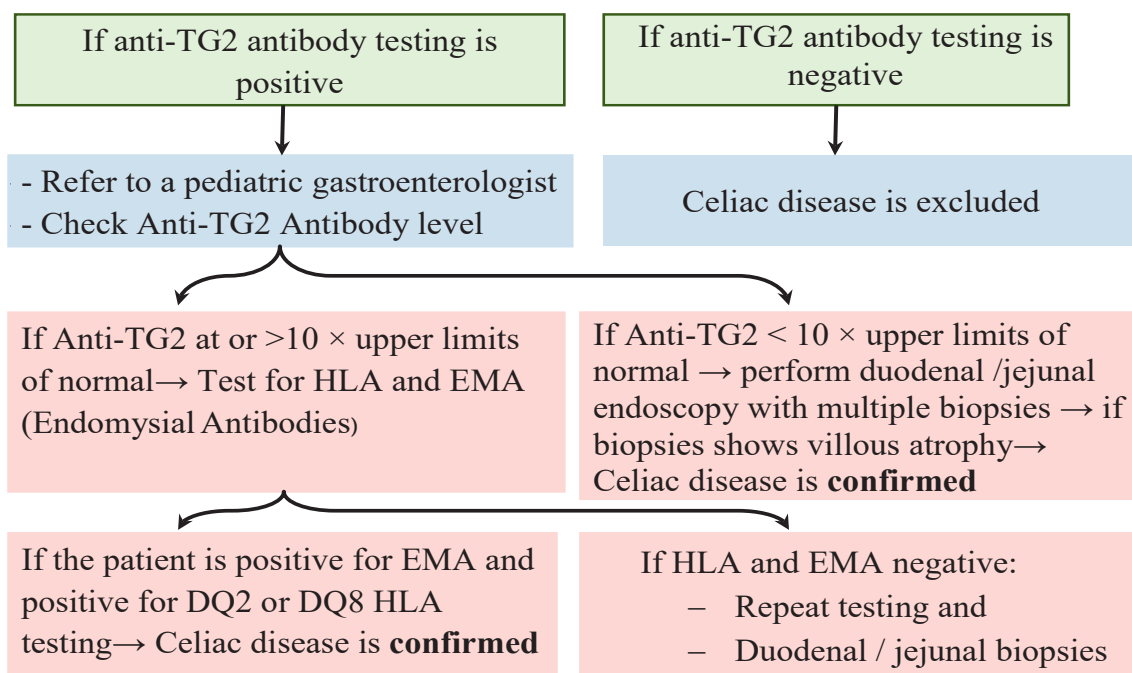
- No apparent symptoms in spite of histologic evidence of villous atrophy
- In most cases identified by serologic screening in at-risk groups

Potential

- Subjects with positive celiac disease serology but without evidence of altered jejunal histology

Diagnosis**1. Symptomatic patients**

Test for IgA anti Tissue Trans Glutaminase 2 antibodies (anti-TG2 IgA antibodies) and in addition for total IgA in serum to exclude IgA deficiency

**2. In asymptomatic cases:** diagnosis of celiac is determined by biopsy**3. Diagnosis confirmation:**

Diagnosis is confirmed by an antibody decline, and preferably, a clinical response to a gluten-free diet.

4. If diagnostic uncertainty remains:

Gluten challenge and repetitive biopsies

Treatment

- Lifelong strict adherence to a gluten-free diet (use maize & rice) regardless of the presence of symptoms with aid of an experienced dietician
 - Monitoring for symptoms, growth, physical examination, and adherence
 - Periodic measurements of TG2 antibody levels to document reduction in antibody titers
- (ESPGAN 2013, Nelson textbook of pediatrics)

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Self-Assessment Case Scenarios**Case 1**

A male patient aged one-year presented to the ER room with history of severe watery diarrheal attack two days back but with minimal vomiting but since this morning vomiting becomes more intractable with loose stool with mucous and blood. On examination, he was crying with sunken eyes, severely irritable, temperature 38°C, thready pulse and moderate dehydration.

- a. What is the diagnosis?
- b. Investigations?
- c. Management?

Case 2

A 9 months old baby girl, formula fed, presented to you with vomiting and diarrhea for previous 12 hours. On examination she was found lethargic, deeply sunken eyes, skin recoil after more than 2 seconds and capillary refill time >3 seconds (normal < 2 seconds). Her current weight is 5.5 kg

- a. What is the degree of dehydration?
- b. What should be initial line of treatment?

Case 3

An 18 month old male is brought to the emergency department with a chief complaint of diarrhea and vomiting for 2 days. His mother describes stools as liquid and foul smelling, with no mucous, or blood. He reportedly is unable to keep anything down, vomiting after every feeding, even water. He has about 6 episodes of diarrhea and 4 episodes of vomiting per day. He has a decreased number of wet diapers. Exam: temp 37.0, Pulse 110, RR 25, BP 100/75, weight 11.3 kg (40th percentile). He is alert, in mother's arms, crying at times, and looks tired. Minimal tears, lips dry, mucous membranes tacky, His diaper is dry. No rashes are present. His capillary refill time is less than 3 seconds and his skin turgor is slightly diminished.

- a. What is the degree of dehydration
- b. How far ORS is suitable for this baby?
- c. What are amount of required fluids?

(Source: Case Based Pediatrics, Hawaii University)

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Infections

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الدفعة الـ 14

Scarlet fever

Etiology

- * Group A β hemolytic Streptococci (GAS) that produce erythrogenic toxin
- * Transmitted by droplet infection
- * Incubation period: 3 days

Clinical picture

Throat

- Sudden onset of fever and sore throat
- Tonsils are red, enlarged with patches of exudates which may form a membrane
- Pharynx is red and edematous



Tongue

- In the 1st two days:
White strawberry tongue (white coated tongue with red edematous papillae)
- By the 5th day:
Red strawberry tongue (shedding of the white coat leaving red tongue with prominent papillae)



Skin rash

- Diffuse red maculopapular, fine punctate → Goose skin appearance.
- Appears on the 2nd day of the disease.
- Starts in around neck then spread to the trunk.
- Rash is more intense in deep creases (e.g. elbow) → and don't blanch on pressure (Pastia's Lines).
- In the face; it spares the peri oral area → Flushed face with circum oral pallor
- Rash fades with peeling at the fingers and toes after 3- 7 days



Investigations

- Leucocytosis with neutrophilia
- Rapid antigen test is very specific with 85-95% sensitivity
- Positive throat culture.
- Anti Streptolysin O (ASO) titer >250 Todd units ;peaking in the second week

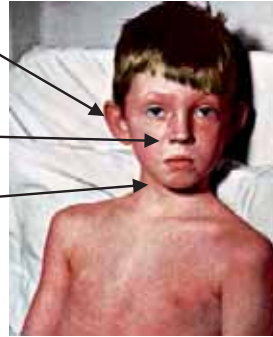
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Complications

- **Early (suppurative; septic);** in the 1st week of illness

A. Local

- Acute otitis media, mastoiditis
- Sinusitis
- Retropharyngeal abscess
- Cervical lymphadenitis



B. Distant(rare)

- Meningitis
- Bronchopneumonia
- Arthritis
- Septicemia

- **Late (non suppurative; aseptiC):** after a latent period (2-3 weeks)
 - Acute rheumatic fever
 - Acute glomerulonephritis
 - Post streptococcal reactive arthritis (non migratory, small and large joints)
 - Erythema nodosum ; red, raised, tender nodules over the chin of the tibia
 - Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus pyogenes (PANDAS) includes tics disorders, obsessive compulsive disorders and Tourette syndrome

- **Chronic carrier state**

Differential diagnosis

a. Other causes of tonsillar membrane

- Infectious mononucleosis (clue: lymphocytosis and ↑transaminases)
- Oral moniliasis
- Agranulocytosis

b. Viral pharyngitis

1. Pharyngoconjunctival Fever:
 - Caused by an adenovirus and often is epidemic.
 - Exudative tonsillitis, conjunctivitis, lymphadenopathy, and fever are the main findings.
 - Treatment is symptomatic
2. Other causes of viral pharyngitis ; suggested by presence of conjunctivitis, cough, hoarseness, symptoms of upper respiratory infection, anterior stomatitis, ulcerative lesions, viral rash, and diarrhea

c. Other causes of strawberry tongue

- Kawasaki disease
- Staphylococcal toxic shock syndrome
- Streptococcal toxic shock syndrome

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Treatment

1. Symptomatic: bed rest, light diet, anti-pyretic and adequate fluid intake.
2. Antibiotics options
 - Oral penicillin V for 10 days
 - Once daily amoxicillin (50 mg/kg, maximum 1,000 mg) for 10 days
 - Single intramuscular injection of benzathine penicillin G
 - Erythromycin or azithromycin for penicillin sensitive patients

3. Eradication of carrier state:

It is not usually required unless the patient or another family member has frequent streptococcal infections

Or

If a family member or patient has a history of rheumatic fever or glomerulonephritis

Use: Clindamycin for 10 days or Rifampin for 5 days

N.B: In the past, daily penicillin prophylaxis was occasionally recommended; however, because of concerns about the development of drug resistance, tonsillectomy is now preferred for patients with recurrent streptococcal tonsillitis

(Current Pediatrics)

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الدفعة الـ 14

Pertussis (whooping cough)

Etiology

- Organism: Bordetella pertussis & Bordetella parapertussis
- Route of infection: Droplet infection (mainly in child < 5 years)
- Incubation period: 1-2 weeks.

Clinical picture

1. Catarrhal stage

- The most infectious stage (1-2 weeks)
- Coryza
- Conjunctivitis
- Cough
- Mild fever



2. Paroxysmal stage

- Lasts for 4- 6 weeks up to 10 weeks
- Paroxysms of cough
 - Series of > 5 cough in single expiration followed by a whoop (forcible inspiration against narrow glottis).
 - During the attack; there's facial redness, bulging eyes, tongue protrusion and distended neck veins.
 - Post tussive vomiting is very common
 - After the attack; patient appears drowsy and exhausted.
 - Paroxysms may be triggered by eating, drinking , and exertion
 - Paroxysms are more worse at night



3. Convalescence stage

- Lasts for 1-2 weeks
- Gradual decline in severity of paroxysms but cough may last for months

Complications

More frequent in infants and young children

1. Secondary infection

- Bronchopneumonia / pneumonia usually with staphylococci or streptococci
- Otitis media
- Activation of dormant tuberculosis infection
- Atelectasis

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2. Seizures; may be due to:

- Cerebral hypoxaemia
- Intracranial hemorrhage.
- Tetany (severe vomiting → alkalosis → ↓ ionized Calcium)

3. Straining in paroxysms can lead to

- Sub-conjunctival hemorrhage
- Epistaxis
- Intracranial hemorrhage
- Ulcers of tongue frenulum.
- Pneumothorax
- Hernias ; umbilical & inguinal.
- Rectal prolapse.

**4. Malnutrition**

Due to anorexia , vomiting , and faulty food restriction

Diagnosis**In catarrhal stage**

- History of contact with to a typical case
- Nasopharyngeal swab and direct fluorescent antibody staining
- Nasopharyngeal swab and PCR or Culture

In paroxysmal stage: Typical paroxysm with:

- Absent fever, wheezes or rales
- Cough ≥ 14 days
- Apnea in infants less than 3 months

Differential diagnosis: from other causes of:**a. Spasmodic cough:**

- 1 Pertussis
2. Adenovirus infection; associated with sore throat and conjunctivitis.
3. Foreign body inhalation
4. Pneumonia: Interstitial or Mycoplasma
5. Mediastinal mass e.g. lymph node compressing the trachea.
6. Bronchiolitis

b. Other causes of chronic cough e.g.

1. Bronchial asthma: - Recurrent wheezy chest
 - Related to allergens or exercise
 - Respond to bronchodilators
 - Relatives with asthma
2. Pulmonary tuberculosis

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Treatment

1. Cases

a. General

- Isolation and Bed rest
- Avoid triggers of cough(e.g. hyperactivity)
- Cough sedatives
- Care of feeding: small frequent feeds or tube feeding

b. Antibiotic

*** Values**

- Reduction of infectivity period
- Possible clinical improvement.

*** Choice**

- Azithromycin 10 mg/kg/day for 5 days
- Clarithromycin 15 mg/kg/day for 7 days
- Erythromycin 50 mg/kg/day for 10 days

2. Prevention

- Active immunization : DTaP vaccine
- Antibiotic as for contacts regardless immunization state ± Booster dose of DTaP
- Intra muscular pertussis immunoglobulin for contacts below 2 years

Self assessment case scenarios

Case 1

An infant aged 29 days was taken by her parents to a local emergency department with difficulty breathing. The infant had been coughing for approximately 5 days with increasing severity, resulting in post tussive vomiting and several choking episodes. At presentation, the infant was lethargic, and examination revealed tachycardia and mild fever. He had thick, foamy mucus coming from his mouth, appeared cyanotic, and had an O2 saturation of 70%. Laboratory results revealed severe lymphocytosis and a chest radiograph revealed perihilar infiltrates

The infant's mother, aged 20 years, has a prolonged paroxysmal cough with post tussive vomiting and gasping for air that began approximately 3 weeks before the infant's delivery

a. What is the diagnosis?

b. How to confirm diagnosis?

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Enteric Fever (typhoid fever)

Etiology

- Organism: *Salmonella typhi* & *paratyphi* (A,B,C) ⇒ G-ve bacilli
- Route of infection: faceo-oral route from cases or carriers
- Incubation period: 2 weeks

Clinical picture

1. In young infants

- Acute onset of fever , vomiting , and diarrhea
- A picture mimic bacillary dysentery and dehydration

2. In older child: Like adult typhoid

Fever

- Has a stepladder rising pattern ; plateau at 39-40 C° by the end of 1st week
- Associations
 - Headache, prostration , anorexia , chills and dry cough
 - Coated tongue
 - Relative bradycardia

Abdominal

- Diffuse abdominal pain
- Diarrhea (*Pea-soup*) may occur early → but constipation predominates later
- Splenomegaly : small , soft and tender
- Rose spots :
 - Salmon-colored, blanching, truncal, maculopapules
 - Appear by the 5th day and resolve within 5 days



Outcome

- * By the end of the 1st week the patient may appear acutely ill , lethargic with convulsions (*status typhosus*)
- * Convalescence starts after 4 weeks by decline in temperature and improvement of the general condition .
- * Relapse may occur within 4 weeks from decline of fever

Complications

• Gastro intestinal

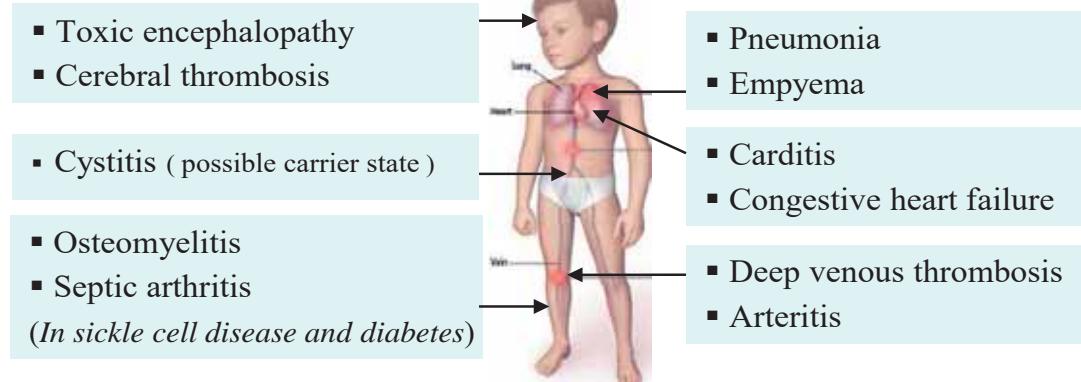
- Intestinal hemorrhage and perforation by end of 2nd week
- Cholecystitis (possible carrier state)
- Perisplenitis



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– Gastroenteritis → dehydration and electrolyte disturbances

• **Other rare complications**



Relapse; May occur within 4 weeks from drop of temperature

Diagnosis

- The mainstay of diagnosis of typhoid remains clinical in much of the developing world
- Blood culture is positive in 40-60% of cases early in the disease
- After the 1st week
 - a. Widal test (Positive titer >1/160)
 - Detect antibodies against O & H antigens
 - Never used alone to prove the diagnosis in endemic areas
 - b. Positive stool culture and urine culture
- Other investigations:
 - a. CBC:
 - Anemia & leucopenia (toxic depression of bone marrow).
 - Thrombocytopenia is a marker of severity
 - b. Nested polymerase chain reaction analysis using H1-d primers has been used to amplify specific genes of *S. Typhi* in the blood of patients
 - c. Culture of bone marrow cells (not affected by prior use of antibiotics but invasive)

Treatment

1. Cases

a. General

- Bed rest & light diet
- Symptomatic treatment
- Treat complications:
 - Intravenous line and intravenous fluids for shock
 - Blood transfusion for hemorrhage
 - Surgical consult for intestinal hemorrhage and/ or perforation

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b. Antibiotics choice

- For fully sensitive and uncomplicated enteric fever
 - Chloamphenicol or ampicillin for 14-21 days (high relapse rate) or
 - Alternative: Flouroquinolone
- For multidrug resistant (*to ampicillin, septazole, and chloramphenicol*)
 - Flouroquinolone or
 - Cefixime or Ceftriaxone
- For quinolone resistant enteric fever
 - Azithromycin for 7 days or
 - Ceftriaxone for 10-14 days

2. Prevention

- Food & water hygiene
- Vaccine → Ty21a or Vi capsular conjugate vaccine (TAB vaccine is obsolete)

Self assessment case scenarios

Case 2

A 12-year-old child developed fever about 1 week after visiting relatives in the village. The fever has persisted for about 10 days. Diarrhea was present for a few days, and then cleared. The child is now constipated. The child appears moderately acutely ill. The liver and spleen are enlarged. There are palpable, small (2–4 mm) erythematous spots on the trunk only.

What is the most likely cause of this child's infection?

Case 3

A seven-year-old girl presented to our hospital with fever, abdominal pain, nausea, vomiting and diarrhoea for one week duration, followed by fresh bleeding per rectum after 10 days from her illness. She had history of neither chronic medical disease nor surgical operation. Physical examination on admission revealed pallor, BP = 80/50 mmHg, pulse rate = 97 b/m, rapid respiration, temperature = 40.2 °C. Her abdominal examination revealed mild splenomegaly with diffuse abdominal tenderness. Blood profile showed a hemoglobin of 7.1 g/dl, and white blood cell of 4500

An urgent colonoscopy revealed multiple variable size punched-out ileal ulcers

a. What is the diagnosis?

b. What are the important four lines of management?

(Journal of Medical Case Reports 2010, 4:171)

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Tetanus (Lock Jaw)

Etiology

Clostridia tetani (gram positive spore forming, anaerobic bacilli)



Spores excreted in animal excreta → contaminate soil and water



Contaminate wounds, umbilical stump, surgical & vaccine sites



Spores germinate → proliferate locally → produce 2 toxins (tetanospasmin & tetanolysin) which travel along nerve trunk & blood stream



Reach the CNS then redistribute to spinal cord, brain & motor end plate.

Clinical picture

Incubation period: 1-14 days but may be longer

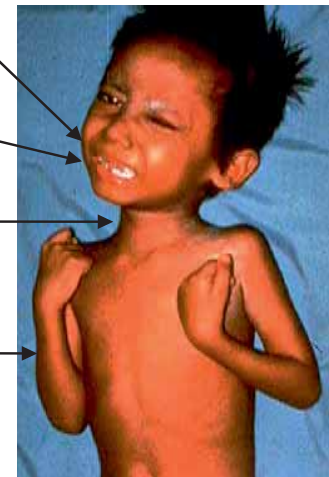
1. Mild tetanus

- * Pain & stiffness at site of injury for few weeks
- * Occur in patients who received the antitoxin before
- * Mortality < 1%

2. Generalized tetanus (typical form)

- * Spasms occur in descending form with intact consciousness:
- * Spasms precipitated by visual or auditory stimuli

- **Risus sardonicus** : grimacing face due to facial muscles spasm
- **Trismus**: difficult mouth opening due to masseter spasm.
- **Laryngeal spasm** → stridor and may be suffocation
- **Opisthotonus** → arched back
- **Tonic seizures** → flexed adducted arms and extended lower limbs with clonic



3. Cephalic tetanus

- Follow head injury or otitis media.
- Short incubation period with high mortality
- Involve cranial nerves palsy.
- May be followed by generalized form

4. Tetanus neonatorum (due to contaminated newborn's umbilical stump)

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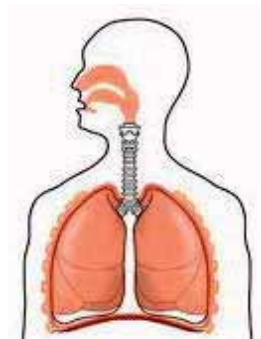
Complications

a. Respiratory

- Laryngeal spasm → suffocation
- Aspiration pneumonia
- Pneumothorax
- Lung collapse.

b. Mechanical: (with severe seizures)

- Tongue laceration
- Vertebral fractures
- Muscle hematoma.



Diagnosis

- 1- History of wound and typical spasms
- 2- Normal CSF.
- 3- Wound culture may be helpful.

Treatment

I. Prevention

1. Active immunization

- DTaP or DT At 2, 4, 6, 18 months
- Booster dose at 4 years

2. Prevention of tetanus after injury:

- a. Surgical management of the wound (better left opened.)
- b. Prophylaxis as follows (according to immunization history):-

1. Unknown or received less than 3 doses of toxoid

- * Booster dose of diphtheria toxoid vaccine
- * Tetanus immunoglobulin(500units) or tetanus antitoxin(5000 units) for contaminated wounds

2. If received 3 doses or more of toxoid

Ask for the time of last toxoid dose:

- * In clean wounds
 - Last toxoid dose ≥ 10 years → booster dose
 - Last toxoid dose < 10 years → nothing
- * In contaminated wounds
 - Last toxoid dose ≥ 5 years → booster dose
 - Last toxoid dose < 5 years → nothing

3- Prevention of tetanus neonatorum:

- Maternal immunization with tetanus toxoid
- Aseptic care of the umbilical stump

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II. Curative

- 1- The patient is kept in quiet, dark room.
- 2- Supportive → I.V fluids
→ Respiratory Care:
 - Suctioning.
 - Keep patent airway
 - Oxygen inhalation
 - May need assisted ventilation.
- 3- Diazepam I.V for spasms (0.1 – 0.3 mg/kg)
- 4- Toxin neutralization
 - Tetanus immunoglobulin 3000-6000 IU
 - Anti tetanic serum (tetanus antitoxin) 50.000-100.000 IU
- 5- Penicillin G 200.000 IU/kg/d I.V for 10 days.
- 6- Immunization after recovery

Self assessment case scenarios

Case 4

A seven-day-old male baby was admitted to the Intensive Care Unit with progressive difficulty in feeding, hypertonicity, and severe tonic contractions of the muscles triggered by minimal stimuli such as light, noise or touch.

The patient was afebrile and eupneic, weighing 2800 g, and had a history of nonsterile home delivery. The laboratory evaluation was within normal except for Culture from the umbilical cord grew several aerobic bacterial species



(a)



(b)

1. What is the diagnosis?
2. What are the clinical signs seen?

Case 5

A 5-year-old unimmunized child fell while playing in an old barn and sustained a laceration to his leg. After local wound care, what would be the most appropriate management regarding tetanus prophylaxis?

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Viral Infections

Measles (Rubeola)

Etiology

- RNA virus One antigenic type, so, one attack gives lifelong immunity
- Transmitted by droplet infection.
- Incubation period 1-2 weeks
- Infectivity period 5 days before & 5 days after rash

Clinical picture

a. Catarrhal stage

- High fever
- Non purulent conjunctivitis with photophobia.
- Coryza (mucopurulent rhinitis)
- Cough (dry, irritating, barking)
- Sore throat



Koplick's spots (pathognomonic)

- Appear on the 3rd day of fever
- Opposite the lower molar teeth
- Grayish white dots with red areolae.
- Disappear 2 days after rash



b. Eruptive stage

1. Fever /rash relationship

- Rash usually appear on the 4th day of fever
- Fever rises up to 40 °C for 2 days then rapidly fall

2. Rash pattern

- Maculopapular rash
- Starts behind the ears near the hair line
- By the 1st day it covers the upper half of the body
- By the 2nd day it covers the lower body till the thigh
- By the 3rd day it reaches the feet When it reaches lower limbs, it fade from the face over the next 3 days





c. Convalescence stage

Rash fade in order of appearance with fine branny desquamation (except in palms & soles)

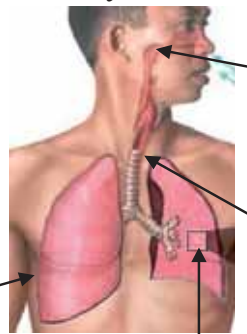
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Measles variants

Modified (attenuated) measles	Atypical measles
	
<p>Seen in patients with preexisting but incompletely protective anti-measles antibody e.g.</p> <ul style="list-style-type: none"> - Receipt of intravenous immunoglobulin - Measles vaccination 	<p>Seen in patients who received killed measles vaccine (obsolete) and in immune compromised</p> <ul style="list-style-type: none"> - Confluent bullous or hemorrhagic rash - Bleeding rash and orifices - Multi organ involvement

Complications**1. Pulmonary infections**

- Commonly 2^{ry} bacterial infection mainly with strept pneumoniae
- with streptococci
- Suggested by:
 - Marked increase of fever decline
 - Malaise and prostration
 - Leucocytosis



- Otitis media
- Sinusitis
- Tonsillopharyngitis

- Laryngitis
- Tracheobronchitis

- Pneumonia

- Hect's pneumonia : viral pneumonia with multinucleated giant cells in the lungs.
- Activation of T.B focus : due to temporary loss of hypersensitivity to tuberculo protein for 4-6 weeks

2. Gastrointestinal complications

1. Ulcerative stomatitis up to cancrum oris
2. Enterocolitis
3. Gastro enteritis

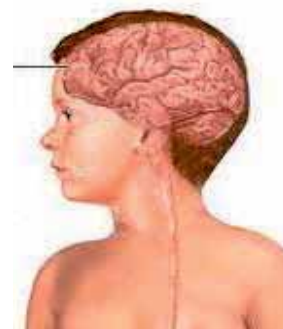
Measles may be complicated by malnutrition



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3. Neurologic complications (Rare)

- Viral encephalitis with a CSF pleocytosis
- Acute disseminated encephalomyelitis during the recovery phase of measles
- Subacute Sclerosing Panencephalitis(SSPE); slow virus infection which manifest years after measles attack
- Guillian Barre syndrome
- Aseptic meningitis.
- Transverse myelitis



Others (Rare)

- Myocarditis, DIC, thrombocytopenia

Prevention

- Measles vaccine at 9 months
- MMR vaccine 1st dose at 12-18 months
- MMR vaccine 2nd dose at 36 months (in USA at school age; 4- 6 years)

Treatment

a. For cases

Treatment is largely supportive; no specific therapy is of proven benefit

1. Supportive

- Bed rest and isolation till rash disappear
- Symptomatic e.g. eye care, paracetamol
- Care of feeding : soft diet , fluids.

2. Treat complications e.g. Antibiotics for 2ry infection

3. WHO and UNICEF recommend single oral dose of vitamin A 100.000 - 200.000 IU to reduce measles morbidity for children with measles complications or at risk for complications

b. For contacts

- Exposed contacts with high risk of complications
 - This groups include infants < 1 year of age, and immunocompromised hosts
 - Intramuscular immune serum globulin can prevent measles if given within 6 days of exposure
 - Live vaccination is given 3 months later
- Exposed contacts without high risk of complications: can be given live measles vaccine within 72 hours of the exposure better than the immunoglobulin

(The American Academy of Pediatrics, the American Academy of Family Physicians, UpToDate website)

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Rubella (German measles)

Etiology

- RNA virus One antigenic type, so, one attack gives lifelong immunity
- Transmitted by droplet infection/ Transplacental
- Incubation period 2-3 weeks
- Infectivity period 7 days before & 7 days after rash

Clinical picture

a. Catarrhal stage

- Mild fever and mild nasopharyngitis
- Characteristic tender enlargement of posterior cervical & post auricular lymph nodes is ;appear 1 day before the rash and last for up to 1 week



b. Eruptive stage

1. Fever /rash relationship

- Rash appears on the 2nd day of fever.
- Fever drops when the rash appear

2. Rash pattern

- Maculopapular similar to measles's but less intensely red (*Rubella is a Latin word for "little red"*)
- Starts in face then involve trunk & limbs
- When reaches the trunk, it fades from the face
- Fades on the 3rd day (3 days measles) without desquamation



Complications

- Congenital rubella syndrome if the mother catches infection during pregnancy especially in 1st trimester
- Other rare complications: Thrombocytopenia, encephalitis, and arthritis.

Prevention: MMR vaccine (see before)

Treatment

1. For cases : Symptomatic care

2. For exposed pregnant :Test immediately for maternal rubella Antibody IgG

- If positive → she is immune →continue pregnancy with close follow up
- If negative and remained negative in subsequent tests → infections hasn't occurred
- If negative initially and turned up positive in subsequent tests either
 - Termination of pregnancy (Better and recommended)
 - If mother declined termination; rubella immune globulin may be given (may reduce severity of fetal infection) (CDC and UpToDate 2012)

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Roseola Infantum

Etiology

- Human herpes type 6 virus (DNA virus)
- Transmitted by droplet infection
- Incubation period: 5-15 days
- Peak age: 5-15 months (*Infantum*)

Clinical picture

1. Fever /rash relationship

- Abrupt high fever up to 39-40 °C
- Febrile convulsion is common
- Fever fall by crisis at the 3rd – 4th day of illness
- Rash appears 12-24 hours after fever's drop

2. Rash pattern

- Maculopapular; rose-like rash (*Roseola*)
- Starts on the trunk → then rise to involve neck, face & lower limb.
- Rapidly fades in 2 days without desquamation



Treatment

- Symptomatic
- Ganciclovir for complicated cases (very rare)

Erythema Infectiosum

Etiology

- Human Parvo B19 virus (DNA virus)
- Transmitted by droplets infection and transplacental
- Incubation period 5-15 days

Clinical picture

- Mild catarrhal stage followed by
- Sudden livid erythema of cheeks (*slapped cheeks*)
- Maculopapular rash follows starting on the trunk
- The rash fades with central clearing (*lacy appearance*)



Complications

- Transient arthritis/arthritis
- Erythroblastopenic crisis in patients with chronic hemolytic anemia

Treatment

- Symptomatic
- IVIG for immunodeficient and chronic hemolytic anemia patients

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Infectious mononucleosis (Glandular fever)

Etiology

- Epstein Barr virus (DNA, oncogenic virus)
- Transmitted by droplet infection and rarely blood borne
- Incubation period : 1 – 2 months
- The virus infect the epithelium then establish in B-lymphocytes

Clinical picture

- Fever , severe fatigue and sore throat
- Tonsillopharyngitis with thick white tonsillar membrane
- Lymphadenopathy(90%) commonly affect cervical group but may be generalized
- Maculopapular skin rash in 15% but in up to 80% of patients if ampicillin or amoxicillin are given
- Mild splenomegaly (50% of cases)
- May be hepatitis and hepatomegaly (10%)



Complications

- Upper airway obstruction by enlarged tonsils
- Rupture spleen; even with minor trauma
- Hematologic disorders: Aplastic anemia, auto immune hemolytic anemia and thrombocytopenia
- Pneumonia
- Myocarditis
- Oncogenicity e.g. nasopharyngeal carcinoma & Burkitt's lymphoma

Investigations

- Absolute lymphocytosis (lymphocyte count $>4500/\text{mm}^3$) & atypical lymphocytes $>10\%$
- Positive heterophile antibody test ; antibodies that agglutinate sheep RBCs (Paul Bunnell test) or horse RBCs (Monospot test)
- EBV IgM antibody or EBV capsid antigen only for heterophile test negative

Treatment

- Symptomatic treatment: antipyretics (avoid aspirin) and bed rest
- Avoid contact sports in the first 2-3 weeks (to avoid rupture spleen)
- Steroids for:
 - Tonsillar enlargement with upper airways obstruction
 - Auto immune hemolytic anemia and thrombocytopenia
 - Seizures and meningitis
- Treatment of complications

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Differential Diagnosis of Maculopapular Rash

1. Viral Exanthema e.g.

- Measles
- Rubella
- Roseola infantum
- Erythema infectiosum
- Infectious mononucleosis.

2. Bacterial Exanthema e.g.

- Scarlet fever
- Typhoid fever
- Meningococcaemia (Toxemia, blood culture, CSF examination)

3. Rickettsial infections

4. Collagen vascular disorders

- Kawasaki disease
- Systemic lupus erythematosus
- Systemic onset rheumatoid arthritis

5. Allergic

- Serum sickness and drug eruption : History of drug intake ,itching

6. Insect bites (e.g. fleas) → Itching ; insect may be seen

→ Lesions fade on pressure.

Kawasaki Disease (KD) : Vasculitis of medium and small-sized blood vessels

Diagnostic criteria

- Prolonged unexplained fever of $>38.5^{\circ}\text{C} \geq$ five days plus at least 4 out of:
 - Bilateral non exudative conjunctivitis
 - Mucositis: cracked, red lips , a strawberry tongue and injected pharynx
 - Polymorphous rash: perineal erythema, followed by macular, morbilliform, or targetoid skin rash of the trunk and extremities
 - Extremity changes: edema of the dorsum of hands and feet, and a diffuse erythema of palms and soles
 - Cervical lymphadenopathy; at least one lymph node >1.5 cm in diameter.
- KD carries risk of coronary aneurysms and infarction

Investigations

- Elevated acute phase reactants and thrombocytosis
- Echocardiography follow-up for coronary aneurysms

Treatment

- IVIG 2gm/kg IV infusion over 8-12 hours
- Aspirin oral 80-100 mg/kg till fever decline for 48 hours then antiplatelet dose 3-5mg/kg till acute phase reactants normalizes

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Self assessment case scenarios

Case 6

A 17-month-old nonimmunized girl has had fever for 4 days and coryzal manifestations followed by a maculopapular rash. Once she developed the rash, the temperature shoots to 40 C for 2 days. Throat examination showed grayish white spots over the inner aspect of the cheek. There is a 4-month-old sibling at home.

What is the appropriate management for this sibling?

Case 7

A pregnant mother in the 1st trimester brought her 8 years old girl who had fever and mild coryzal manifestations for 2 days. Fever immediately settled the time a skin rash appeared. On examination the girl was entirely normal apart from faint rosy maculopapular rash over the face and upper chest along with tender bilateral post auricular lymph nodes

- a. What exanthema disease does this girl have?
- b. What is the appropriate advice for her mother?

Case 8

14-year-old girl presented with a one-week history of fever 38 C, sore throat, progressive fatigue, malaise with mild bilateral posterior cervical adenopathy. Sclera jaundice was prominent. The abdomen was remarkable for moderate hepatomegaly and splenomegaly. Laboratory findings revealed hemoglobin 12 g/dL; platelet count 69.000/mm³; white blood cell count 8.400/mm³ with 10% atypical lymphocytes. Liver function tests reported AST 368 IU/L; ALT 319 IU/L, albumin 3.3 g/dL. Total bilirubin was 4.0 mg/dL and direct bilirubin was 2.4 mg/dL

- a. What are the most important 4 investigations?
- b. What is the diagnosis?

Case 9

This is a 5 year old male who is referred to your clinic by the school nurse for suspicion of child abuse because the child's face appears to have been "slapped" repeatedly. The child has been checked up regularly and is up to date on immunizations. On examination; Temperature is 38.2 C , slight erythema of his oropharynx and pinkish red color of his cheeks. Further questioning reveals an ill cousin with a "rash." Over the next several days, the malar erythema begins to fade and a faint pink rash appears on his trunk and extensor surfaces of his upper extremities. The truncal rash becomes confluent, creating a lacy appearance. Both the fever and rash disappear without any further problems

- a. What is your diagnosis?
- b. What is the etiology?

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Chicken pox (Varicella)

Etiology

- Varicella Zoster Virus(VZV): DNA human herpes virus which can cause varicella in children and Herpes Zoster (**shingles**) if reactivated
- Transmission : - Droplet infection from cases
- Contact with skin lesions from cases
- Incubation period: 2-3 weeks
- Patients are infective 2 days before the rash and till the rash crusted

Clinical picture

- **Prodroma**
 - Fever, malaise, anorexia may occur 24-48 hours before the rash
 - These symptoms resolve within 2-4 days after the onset of the rash
- **Rash**

Appear first	- On the scalp, face, or trunk
Distribution	- Centripetal with little involvement of the limbs
Pattern	- Erythematous macules → evolve into papules → vesicles (tear drop on a base of erythema) → crusts (and pustules may form)
Characteristics	- Simultaneous presence of lesions in various stages - Very itchy rash - In mucus membranes → vesicles may ulcerate

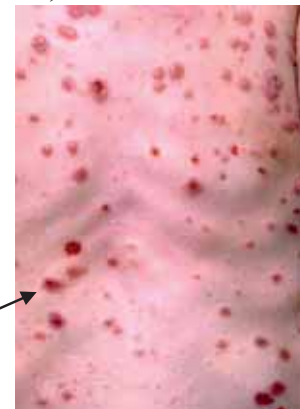


Complications

1. Secondary bacterial infection of the vesicles (in 5% of cases)
2. Progressive varicella may occur in
 - Adolescents and adults even healthy !
 - Immunocompromised children
 - Newborns

Manifestations

- Visceral organs involvement
- Coagulopathy , and severe hemorrhage
- Hemorrhagic vesicles(*Hemorrhagic varicella*)
- Severe abdominal pain(involved mesenteric lymph nodes or the liver)
- Fatal course if adrenal hemorrhage occur



(American academy of pediatrics)

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3. Other rare complications

- Mild thrombocytopenia and transient petechiae may occur in 1-2 %
- Rye's syndrome ; especially with concomitant Aspirin
- Meningoencephalitis and cerebellitis → transient cerebellar ataxia
- Viral pneumonia
- Viral myocarditis

4. Congenital varicella

- If pregnant mother catches infection in the first trimester
- Clinically: Low birth weight , mental retardation & congenital anomalies

Treatment

1. Prevention: Chicken pox Vaccine

- Live attenuated vaccine.
- Given at 12-18 months age
- Dose: - Single dose between 12 months to 12 years.
- Above 12 years → 2 doses 4 weeks apart
- Protective value up to 95%.



2. For cases

a. General

- Antipruritic : calamine lotion , anti histaminics
- Antipyretic (paracetamol); never use aspirin.
- Antibiotics for 2ry bacterial infection

b. Antiviral

Acyclovir	20 mg/kg/dose, given 4 doses per day, for 5 days
Value	Modify clinical picture and prevent complications
Indications	Children >12 mo of age: <ul style="list-style-type: none"> - With chronic cutaneous or pulmonary disorders - Receiving short-term, intermittent, or aerosolized corticosteroid therapy, - Receiving salicylate therapy
Non indication	Not recommended routinely in the healthy child
Initiation	As early as possible, preferably within 24 hr of the onset of the rash

(American Academy of Pediatrics)

3. Post exposure prophylaxis

a. Chicken pox vaccine

- Given to healthy children within 3-5 days after exposure
- Effective in preventing or modifying varicella especially for household contacts and for outbreak control.

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b. Anti-VZV immune globulin

- Recommended for post exposure prophylaxis for:
 - Immunocompromised children
 - Pregnant women
 - Newborns
- Dose is 1 vial (125 units) for each 10-kg of body weight ,IM
- As soon as possible but within 96 hr after exposure.

c. **Oral acyclovir:** late in the incubation period may be protective (??)

Differential diagnosis of papulo vesicular rash

1. Viral infections
 - Chicken pox
 - Herpes zoster (reactivation of dormant varicella)
 - Herpes simplex
 - Hand, Foot, and Mouth Disease
2. Impetigo contagiosa
3. Scabies
4. Others: Fungal infections, Insect bites, Drug eruption

Hand, Foot, and Mouth Disease

- Caused by Coxsackie A virus (an Entero virus)
- Transmitted by oral-oral or fecal-oral routes
- Clinically
 - Oral mucosal lesions : macules or small vesicles that evolve to painful ulcers
 - Palms or soles lesions: Red macules or papules appear in a linear arrangement. They quickly evolve to form vesicles with a clear, watery appearance
- Management
 - Symptomatic e.g. topical local anesthetics to reduce oral discomfort
 - A diet of vanilla ice cream is the easiest to tolerate



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Self assessment case scenarios**Case 10**

7 years old child was brought to the hospital because of vomiting, lethargy, slurred speech, and difficulty in walking. The patient had been in excellent health until 2 days before admission. His brother had had varicella 2 weeks previously. The physical examination at admission revealed an irritable but cooperative child. A neurological examination revealed no abnormality except for nystagmus upon lateral gaze to either side. His skin shows corps of vesicles and papules mainly on the trunk

- a. What is the initial disease?
- b. What is the complication?
- c. What is the prognosis?

Case11

An 18-month-old child presents to your office with a 2-day history of fever. He is not eating well and the mother tells you that she thinks his mouth hurts. On examination you see 3 mm vesicles on erythematous bases on the soft palate and tonsils. The child also has small vesicular lesions on his palms and soles

- a. What is the diagnosis?
- b. What is the etiology?

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Mumps (Epidemic Parotitis)

Etiology

- RNA paramyxo virus affecting the salivary glands.
- Transmission: Droplet infection from human cases; no carriers.
- Incubation period: 2-3 weeks.

Clinical picture

- About 25-30% are subclinical
- Prodroma ; mild fever, malaise & myalgia
- Acute non suppurative inflammation of salivary glands

a. Parotid gland

- Usually one side precede the other
- Tender parotid swelling → push the ear forward and outward
- Swelling ↑ by teeth clenching and ↓ by mouth opening.
- Hyperemic stenson duct orifice
- Swelling ↑ to maximum over 3 days and ↓ over 5 days



b. Submandibular gland

- Submandibular swelling
- May be with parotitis (Alone in 10 %)
- Less painful



c. Sublingual gland

- Least common
- Submental swelling
- May be with chest wall edema

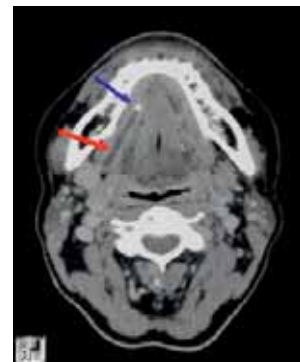
Differential diagnosis

1. Parotid stone (acute obstructive parotitis)

- Pain increase by mastication.
- Stone may be felt under the skin
- Stone can be detected by X-ray or CT
- Swelling may be intermittent.

2. Parotid abscess

- Mainly due to staph aureus.
- High fever.
- Throbbing pain.
- Pus may ooze from Stenson duct orifice.



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3. Endemic parotitis

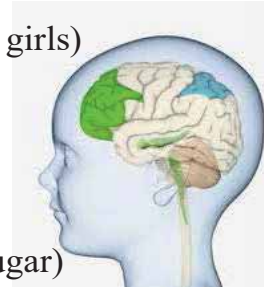
- Bilateral painless swelling of parotids
- Due to malnutrition, ankylostoma, chronic anemia

4. Upper deep cervical lymphadenitis

Complications

1. Meningitis and Meningoencephalitis

- The most frequent complication (10 - 30 % cases; boys > girls)
- Most commonly manifests 5 days after the parotitis
- Clinically
 - Fever, vomiting, headache ,and convulsions
 - Meningeal irritation signs in older children
 - CSF (clear, ↑tension, ↑protein, ↑lymphocytes, normal sugar)
 - In typical cases, symptoms resolve in 7-10 days
 - Aqueduct stenosis and hydrocephalus are rare possible sequels



2. Epididymo- Orchitis

- Commonest complication in adolescents boys and adults
- Usually follow parotitis
- Clinically
 - Fever, chills ,lower abdominal pain
 - Severe testicular pain, accompanied by swelling and erythema of the scrotum
 - Usually unilateral (Bilateral in $\leq 30\%$)
 - Atrophy of the testes and impaired fertility may occur but sterility is very rare even with bilateral involvement



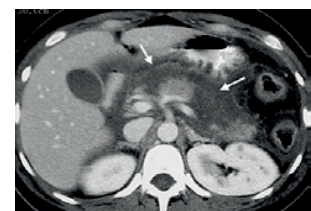
3. Oophoritis

- Uncommon in post pubertal girls
- Clinically
 - Pelvic pain and tenderness
 - May be confused with appendicitis when located on the right side



4. Acute hemorrhagic pancreatitis

- May occur even without parotid swelling
- Features
 - Acute epigastric pain and tenderness
 - Vomiting, fever & prostration
 - ↑ serum lipase is characteristic
 - Abdominal ultrasound and CT scans are diagnostic



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5. Other rare complications

- Sensorineural hearing loss
- Thyroiditis
- Myocarditis
- Migratory polyarthralgia
- Mumps embryopathy(abortion or enocardial fibroelastosis of fetal heart)

Treatment

a. Prevention

- MMR vaccine (see before)

b. Cases

- Isolation: Patients with mumps should stay home from school or work for five days after onset of clinical symptoms, as recommended by the American Academy of Pediatrics (AAP)
- Symptomatic treatment:
 - Topical application of warm or cold packs to the parotid gland may be soothing
 - Analgesics e.g. acetaminophen
 - Soft diet (avoid sour fluids)
- Treatment of complication e.g.
 - Orchitis (support testis ,analgesics)
 - Acute pancreatitis responds to supportive care (IV fluids,electrolytes)
- The local public health officials should also be notified .

Case 12

A 17-year-old male patient was admitted to the emergency unit with nausea and vomiting. On physical examination, the patient was unconscious, had neck stiffness, his temperature was 38°C, his blood pressure was normal; he had bilateral swellings in the parotid regions and findings of unilateral red swollen scrotum

- a. What is the diagnosis?
- b. What is the required investigations?
- c. What is expected from his lab investigation?

Case 13

A 17-year-old male patient was admitted to the emergency unit with nausea and severe vomiting associated with a band-like back pain, shortness of breath, and palpitation. On physical examination, pulse 195 bpm, he had bilateral swellings in the parotid regions. Blood glucose 192 mg/dl , amylase 512 u/l (n 25-125), CPK 1121 u/l (n 38-174), and CK-MB 75 u/l (n 2-6)

- a. What is the diagnosis?
- b. What are the most important investigations?

(Indian Journal of Radiology and Imaging, 2006 ,Volume : 16, Issue : 3, Page : 305-308)

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Poliomyelitis

Causes

- RNA enterovirus with 3 serotypes (I, II, III)
- Transmission: Faeco oral infection or droplet infection
- Outcome of infection
 - Not all infected cases develop the disease
 - Incidence is 1 diseased for 10.000 infected depending on
 - Neurovirulence of the virus
 - Host factors e.g. Extremes of age ,I.M injection

Pathology of the disease

- Damage to the motor nuclei in spinal cord (anterior horn cells) and brain stem → atrophy of muscles supplied by these motor cells.
- Encephalitis may develop in some cases.

Clinical Forms

Listed in order of severity

1. Subclinical infections

2. Abortive poliomyelitis (minor illness)

- The commonest form (80-90%) with mild constitutional manifestations.
- Presentation : Mild fever, rhinitis , sore throat Or Abdominal pain and ,diarrhea

3. Non paralytic poliomyelitis

As abortive plus picture of aseptic meningitis

- Muscle tenderness
- Meningeal irritation: Pain & stiffness in neck, back & extremities
- Tripod sign : ask the baby to sit ; there will be 3 points of support ; buttocks, hands behind & feet in front
- Head drop sign ⇒ If the baby lifted ⇒ head drops backwards due to weak neck muscles
- Urine retention due to bladder paralysis

4. Paralytic poliomyelitis:

Characters of paralysis

- Lower motor neurone ⇒ hypotonia, hyporeflexia with muscle wasting
- Asymmetric ⇒ one limb is affected more than the other.
- Patchy distribution ⇒ affect some groups (esp. the large) sparing others in the same limb.

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Types of paralysis

- Spinal
 - 2^{ry} inability to walk (lower limb muscles)
 - Respiratory failure (respiratory muscles)
 - Scoliosis (trunk muscles)
- Paralysis of medullary nuclei
 - Cranial nerves 9,10,11,12 → Palato-pharyngo-laryngeal paralysis
 - Respiratory center → irregular breathing
 - Vasomotor center → labile blood pressure and dysrhythmias

Diagnosis

Viral isolation Stool Throat

Differential diagnosis

A. Causes of acute flaccid paralysis:

Paralytic disease	Features of paralysis
Guillain Barre syndrome	Symmetric , ascending , motor & sensory
Tick paralysis	Symmetric , ascending , / find the tick
Post diphtheritic	Symmetric , descending, motor & sensory
Botulism	Symmetric , descending / history
Transverse myelitis	Symmetric , non progressive , with sensory level

B. Causes of pseudo paralysis

- Bones: scurvy, osteomyelitis and fractures
- Joints: arthritis, dislocation and synovitis

Management

Prevention: Polio vaccines

Supportive

- Analgesics (avoid injections).
- Bed rest with good diet.
- Care of bladder (parasympathomimetics ± catheter)
- Care of comatose
- Decrease deformity by proper positioning of limbs.
- Enema and laxatives for constipation
- Physiotherapy after 2-3 weeks & orthopedic consultation

Treat complications

- For Bulbar paralysis:
 - Support respiration
 - Monitor blood pressure
 - Care of nutrition

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Parasitic Diseases

Nematodes

- | | | |
|---|------------------|--|
| <ul style="list-style-type: none"> • Ascaris • Enterobius vermicularis • Ankylostoma (hook worm) • Strongyloids | }
}
}
} | <p>Infection occur by.</p> <p>Ingestion of eggs.</p> <p>Infection occur by.</p> <p>Skin penetration by larvae.</p> |
|---|------------------|--|

Clinical features

- Asymptomatic
- Abdominal pain
- GIT bleeding (anemia). } Malnutrition and impaired growth may occur
- In Ankylostoma & Strongyloids → skin penetration may lead to → pruritic maculopapular rash at the site of penetration (Ground itch)
- Ascaris & ankylostoma may lead to pulmonary symptoms due to larval migration
- Ascaris may lead to intestinal obstruction.
- Enterobius (oxyuris) may lead to:
 - Enuresis & irritability
 - Nocturnal anal pruritus

Diagnosis

- Detect the worm or the characteristic eggs in stool.
- Test for complications: occult blood in stool, iron deficiency anemia.

Treatment

- General: hand washing, fingernails kept cut & clean, avoid bare footing.
- Albendazole (400 mg PO once) or Mebendazole or Flubendazole 100 mg twice daily for 3 days
- For oxyuris
 - Single oral dose of Mebendazole (100 mg) or Albendazole (400 mg)
 - Repeat in 2 weeks with treatment of all family contacts
- Nitazoxanide (100-200 mg bid PO for 3 days)give same cure rate as Albendazole
- Ivermectin (Stromectol, Mectizan) is FDA approved for treatment of intestinal Strongyloids

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Schistosomiasis

Life cycle

Exposure to water channels → cercariae penetrate skin which mature into adult worms in 1-3 months which travel to:

- Urinary bladder → *Schistosoma haematopium*
- Intestine → *Schistosoma mansoni*

Adult worms lay eggs when eggs reach fresh water they inhabit the snails to mature into hundreds of cercariae

	<i>Schistosoma haematopium</i>	<i>Schistosoma Mansoni</i>
Incidence	- Prevail in all Egypt	Prevail in lower Egypt
Clinical picture	Pruritic papular dermatitis may occur at site of cercarial entry	
	- Cystitis - Terminal haematuria - Late ⇒ cancer bladder	- Bleeding per rectum - Abdominal pain , diarrhea , tenesmus - Late : liver fibrosis & portal hypertension
Investigation	- Urine analysis for ova - Rectal snip & look for ova - Serology is not accurate	- Stool analysis for ova - Bladder biopsy & search for ova - Serology is not accurate
Treatment	Praziquantel 40 mg/kg/d in 2 divided oral dose (drug of choice)	

Cestodes

	<i>T. saginata</i>	<i>T. solium</i>	<i>H. Nana</i>
Definitive host	Human	Human	Human
Intermediate host	Cattles (beef)	Pigs (pork)	Fleas
Infection	Ingestion of cysticercus bovis in under cooked beef	Ingestion of cysticercus cellulosa in under cooked pork	Ingestion of eggs
Clinical picture	- Abdominal pain - Distension - Weight loss	- Abdominal pain - Distension - Weight loss	- Abdominal pain - Distension - Weight loss - Irritability & fits due to neurotoxins
Treatment	Praziquantel 25 mg /kg single oral dose or Niclosamide : 50 mg/kg PO once for children, 2 g PO once for adults However, this medication is no longer available in the USA		

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Ecchinococcus granulosus

Definitive host	Dogs
Intermediate host	Humans and Cattle
Clinical picture	Eggs change into cysts into the liver(2/3) , lungs, brain→ compression manifestation Rarely cyst rupture → severe anaphylaxis
Treatment	- High dose Albendazole for 6 months - Surgical removal <u>or</u> ultra sonic aspiration for severe pressure manifestations

Diseases Caused By Protozoa

	Amoebiasis	Giardiasis
Etiology	Entamoeba histolytica	Giardia lamblia
	* Inhabit the large intestine. * Exist in two forms: - Cystic form (non invasive) - Vegetative form (invasive).	* Inhabit the upper small intestine * Present in two forms : - Cyst form (non invasive) - Vegetative form (invasive).
Transmission	Feco-oral route	Feco-oral route
Clinically	- Asymptomatic. - Ameobic dysentery - Extra intestinal (Lung & liver abscess)	- Asymptomatic. - Diarrhea - Abdominal distention - Abdominal pain (chronic, recurrent). - May be malabsorption syndrome
Treatment	<u>Asymptomatic intestinal carriers</u> Paromomycin or Diloxanide furoate oral in 3 dose for 7 days <u>Invasive forms</u> ○ Initial Metronidazol 50 mg/k/day (oral 3 doses) for 7-10 days or Tinidazol 50 mg/k/day (oral single dose) for 3 days ○ Followed by 7 days course of oral Paromomycin 25 mg/kg/day	<u>Preferred</u> ▪ Tinidazole 50 mg/k/d single dose ▪ Nitazoxanide 4-11 yr: 200 mg bid for 3 days >12 yr: 500 mg bid for 3 days ▪ Metronidazole 15 mg/k/d for 7 days <u>Alternative</u> ▪ Albendazole 400 mg once a day for 5 days

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Fever

Definition

- A rectal temperature $\geq 38^{\circ}\text{C}$
- A value $>40^{\circ}\text{C}$ is called hyperpyrexia.
- Any abnormal rise in body temperature should be considered a symptom of an underlying condition

Etiology

- **Infectious:**
 - Self-limited viral infections (common cold, gastroenteritis) and uncomplicated bacterial infections (otitis media, pharyngitis, sinusitis) are the most common causes of acute fever
 - Others: urinary tract infections, pneumonia, meningitis,...
- **Inflammatory** e.g. Rheumatic diseases
- **Neoplastic** e.g. Leukemia and Neuroblastoma
- **Miscellaneous** e.g. Familial Mediterranean Fever

Evaluation of acute fever

- Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates), travel, medications, other underlying disorders, immunizations
- Physical examination: complete, with focus on localizing symptoms
- Laboratory studies on a case-by-case basis
 - Rapid antigen testing
 - Nasopharyngeal: respiratory viruses
 - Throat: group A streptococcus
 - Stool: rotavirus
 - Throat culture
 - Blood: complete blood count, blood culture, C-reactive protein, sedimentation rate
 - Urine: urinalysis, culture
 - Stool: hemocult, culture
 - Cerebrospinal fluid: cell count, glucose, protein, Gram stain, culture
- Chest radiograph or other imaging study

(Nelson textbook of pediatrics)

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Fever without focus

Definition

Fever without a focus refers to a rectal temperature of 38°C or higher as the sole presenting feature

Categories

1. Fever of unknown origin
Children with fever documented by a health care provider and for which the cause could not be identified after 3 wk of evaluation as an outpatient or after 1 wk of evaluation in the hospital
2. Fever without Localizing Signs
Fever of acute onset, with duration of <1 wk and without localizing signs

Fever without localizing focus

Common causes

- Viral infection
- Occult bacteremia
- Bacterial infections e.g.
 - Ear infection
 - Urinary tract infections
 - Meningitis
 - Pneumonia
 - Osteomyelitis
 - Septic arthritis

Management

Hospitalize

- Neonates
- Any toxic child

Medical history for

- Appetite
- Activity
- Reactivity to others
- Recent contact with diseased
- Immunization history

Physical examination for

- Look: normal /active (? viral illness) or sick/inactive (? bacterial illness)
- Color and perfusion

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- Level of arousal
- Cry quality

Investigations

- a. CBC for leucocytosis($>15000 \text{ cell/mm}^3$) , bandemia (band cells $>20\%$) or leucopenia ($<5000 \text{ cell/mm}^3$) usually indicate bacterial infections
- b. C reactive protein(CRP) usually negative in viral infections
- c. Urinalysis for leukocyte esterase, nitrite and pyuria ($>10 \text{ WBC/HPF}$)
- d. Stool analysis for cases with diarrhea
- e. Cultures (urine, stool, blood, CSF)
- f. Chest X ray for any infiltrates

Start empiric antibiotics for

1. Neonates
2. Toxic children
3. Young children who have not received Hib and *S. pneumoniae* vaccines and who have a rectal temperature of $>39^\circ\text{C}$ and leucocytosis

Primary Immunodeficiency Disorders

- Primary immune deficiency due to defects in innate or adaptive immunity
- Secondary immune deficiency are acquired by a range of mechanisms, including immunosuppressive drugs, hyposplenism, chronic illness or viral infection e.g. HIV

Warning signs of primary immune deficiency include:

- Four or more new ear infections within 12 months
- Two or more serious sinus infections or pneumonia within 1 year
- Two or more invasive infections (meningitis, osteomyelitis, sepsis)
- Infections that present atypically or with unusual severity
- Recurrent deep skin or organ abscess
- Severe or long-lasting warts or molluscum
- Persistent mucocutaneous candidiasis after 1 year of age
- Episode of infection with an opportunistic pathogen
- Need for intravenous antibiotics to clear infection
- Prolonged/recurrent diarrhoea
- Failure of an infant to gain weight or grow normally
- Complication after live vaccination (disseminated BCG, varicella, paralytic polio, rotavirus)
- Unexplained autoimmune disease
- Positive family history suggestive of primary immunodeficiency

I. Antibody deficiencies

Criteria

- Typically present after 6 months of age.
- Increased susceptibility to bacterial infections such as Streptococcus pneumoniae, H. influenzae, Pseudomonas and Mycoplasma. Also increased susceptibility to enteroviruses and Giardia lamblia

Examples and Presentation	Findings
X-linked Agammaglobulinaemia (Bruton's disease) <ul style="list-style-type: none"> – B-cell development blocked. – Typical presentation 6 months to 5 years with recurrent sino pulmonary bacterial infections – Hypoplastic tonsils 	<ul style="list-style-type: none"> • IgG, IgM, IgA ↓ • Absent B cells • Absent isohaemagglutinins • BTK gene mutation
Selective IgA deficiency <ul style="list-style-type: none"> – Recurrent upper respiratory tract infections at age > 4yrs – Increased frequency of allergies and autoimmunity – May be asymptomatic 	<ul style="list-style-type: none"> • IgA absent, normal IgG, IgM • Normal vaccine responses

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Treatment

- Supportive care : Antibiotics according to cultures and sensitivity
- Periodic immunoglobulin infusions

II. T Cell defects**Criteria**

- Recurrent infections can occur in 1st 4 – 6 mo of life.
- Failure to thrive is common.
- Mostly due to disseminated viral, fungal, parasitic & certain bacterial infections

Example	Findings
DiGeorge syndrome (CATCH 22) <ul style="list-style-type: none"> – Absent/hypoplastic Thymus with variable T-cell immunodeficiency from SCID-like (complete DiGeorge) to normal via a partial deficiency. Presents any time from neonatal with viral and fungal infections. – Cleft palate – Hypocalcaemia (>3 weeks, requiring therapy). – Conotruncal cardiac defect e.g. Pulmonary stenosis – Facial dysmorphic (Abnormal) features 	<ul style="list-style-type: none"> • Lymphopenia (<1500/mm³) • Lymphocyte subsets and proliferation variable • Associated with chromosome 22q11.2 deletion or with CHARGE syndrome
Chronic muco cutaneous candidiasis <ul style="list-style-type: none"> – Impaired T-lymphocytes response to candida antigen although their response to other antigens normal – Chronic candidiasis – Endocrinopathies : Hypoparathyroidism ,Addison, IDDM 	<ul style="list-style-type: none"> • Impaired candida albicans intradermal skin test, otherwise rest of T cell functions and lymphocytes count are normal

Treatment

- Supportive care : Antibiotics according to cultures and sensitivity
- Thymic tissue or stem cell transplantation/Gene therapy

III. Combined immunodeficiency

- Defective both B cells and T cells lymphocytes
- Increased susceptibility to:
 - Bacteria: Streptococcus pneumoniae, Haemophilus influenzae, Gram-negative Enterobacteriaceae and intracellular pathogens such as Salmonella, Mycobacteria, Cryptosporidium, Pneumocystis Jiroveci
 - Viruses: Respiratory (e.g. parainfluenza, RSV), enteric (e.g. rotavirus), systemic (e.g. CMV, EBV)
 - Fungi: Candida species

Example	Findings
Severe combined immunodeficiency (SCID) <ul style="list-style-type: none"> – Development of lymphocytes blocked by genetic defects. – Presents within the first 6 months of life with faltering growth, persistent diarrhoea and recurrent mucocutaneous candidiasis or with severe pneumonitis (viral or <i>Pneumocystis Jiroveci</i>). – Commonly fatal if not recognized and managed early 	<ul style="list-style-type: none"> • Lymphopenia, hypogammaglobulinaemia • Abnormal lymphocyte subsets (absent T cells, +/-B, +/-NK cells – depending on type of SCID) • Various genetic defects
Wiskott–Aldrich syndrome <ul style="list-style-type: none"> – Presents in early infancy, usually with bleeding/ bruising, recurrent respiratory infections, HSV and EBV infections. – Associated with <ol style="list-style-type: none"> 1. Bloody diarrhea, eczema in early infancy 2. Autoimmune manifestations (vasculitis, hemolytic anemia) 3. Malignancy (leukemia, lymphoma, EBV-driven brain tumors) 	<ul style="list-style-type: none"> • Thrombocytopenia with small platelets • Abnormal polysaccharide vaccine responses • IgE↑, IgA↑, IgM↓ • T-cell number and function progressively declining • Mutation in WASP gene
Ataxia telangiectasia <ul style="list-style-type: none"> – Recurrent respiratory infections in 2nd year of life. – Associated with <ol style="list-style-type: none"> 1. Ocular or facial telangiectasia 2. Progressive cerebellar ataxia 3. Increased risk of leukemia and lymphoma 	<ul style="list-style-type: none"> • IgA↓ • Increased radiation-induced chromosomal breakage in cultured cells • α-fetoprotein↑ • Mutations in ATM gene

Treatment

- Supportive care: e.g. Antibiotics according to cultures and sensitivity, Anti-viral agents,...
- Periodic immunoglobulin infusions
- Stem cell transplantation/Gene therapy

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IV. Neutrophil defects

- Defective killing function of phagocytes
- Increased susceptibility to:
 - Bacteria: Staphylococcus, Pseudomonas and other Gram-negative Enterobacteriaceae.
 - Fungi: Candida, Aspergillus species

Example	Findings
Chronic granulomatous disease (CGD) <ul style="list-style-type: none"> – Defect of pathogen killing within macrophage. – Presents usually before 5 years of age with recurrent, deep-seated infections (liver, perirectal or lung abscess, adenitis, osteomyelitis). – Diffuse granulomata in respiratory/gastrointestinal/urogenital tract – Hepatosplenomegaly, lymphadenopathy – Failure to thrive 	<ul style="list-style-type: none"> • Neutrophil oxidative burst absent • Nitro blue-tetrazolium test negative • Molecular defect is X-linked in two thirds and autosomal recessive in one third
Leukocyte adhesion deficiency <ul style="list-style-type: none"> – Leukocytes unable to attach to vascular endothelium and leave circulation. – Typically presents in neonatal period with delayed umbilical cord separation and sepsis. – Recurrent/persistent bacterial or fungal infections with absence of pus, defective wound healing – Periodontitis. 	<ul style="list-style-type: none"> • Neutrophil counts persistently above normal range. • Leukocyte CD18 and D15a expression < 5% • Lack of $\beta 2$ integrin expression

Treatment

- Supportive care: e.g. Antibiotics according to cultures and sensitivity, Anti-viral agents, Anti Fungal, Prophylaxis for pneumocystis jiroveci...
- Granulocyte transfusion
- Stem cell transplantation /Gene therapy

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V. Innate immune defects

Increased susceptibility according to specific defect

<p>Complement deficiency</p> <ul style="list-style-type: none"> – Can present at any age – Severe bacterial infections with <i>Neisseria</i> species in alternative, lectin and early classical pathway deficiencies. – For early classical deficiencies also increased susceptibility to encapsulated bacteria. – Lupus-like disease with classical pathway deficiencies. – Hereditary angioedema (HAE) with C1 esterase inhibitor deficiency. HAE presents typically in mid-childhood (5–10 years) 	<ul style="list-style-type: none"> • Complement function tests • Mannose-binding lectin (MBL) • C4 level invariably low in HAE. • C1 inhibitor protein and function tests confirm HAE
<p>Hyper-IgE syndrome (Job syndrome)</p> <ul style="list-style-type: none"> – Usually presents before 5 years of age but may present later – Mucocutaneous candidiasis in infancy – Recurrent or persistent respiratory infections, pneumatocele formation – Pathological fractures, scoliosis – Eczema – Increased malignancy risk 	<ul style="list-style-type: none"> • IgE↑ • Lymphocyte subsets and proliferations usually normal • Dominant mutations in gene encoding STAT3

Treatment

Supportive care: e.g. Antibiotics according to cultures and sensitivity

Vaccination against capsulated organisms is vital in complement deficiency

(The Science of Paediatrics; RCPCH Mastercourse by Tom Lissuare 2016)

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Vaccinations

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الدفعة ال14

Compulsory Vaccines (As per Egyptian MOH protocol)

	BCG	Oral polio vaccine	DTaP	Hepatitis B vaccine	MMR*
Nature	Live attenuated T.B bacilli (bacilli of Calmette & Gaurin)	Trivalent live attenuated polio virus types 1,2,3 (Sabin vaccine)	Diphtheria & tetanus toxoids with acellular pertussis vaccine (DPT is no longer used)	Recombinant HBs Ag prepared by DNA technology.	Live attenuated measles, mumps and rubella grown in chicken embryo tissue culture
Indications	Compulsory Vaccination Started during the 1 st year of life				
				<ul style="list-style-type: none"> - Chronic blood recipients - IV drug abusers - Hemodialysis patients. 	
Administration	0.05 ml in neonates 0.1 ml in elders Intradermal in left upper arm.	3 drops oral	0.5 ml I.M in left thigh	<ul style="list-style-type: none"> - 0.5 ml before 10th year. - 1 ml afterwards. IM (in left thigh/deltoid)	<ul style="list-style-type: none"> - 0.5 ml S.C in upper right arm
1st doses	In the 1 st 3 months	Zero dose at 0-15 days. 2,4,6 months	2,4,6 months	2,4,6 months (in other conditions 0,1,6 months).	12-18 months
Booster doses	At beginning of every school period for tuberculin –ve	<ul style="list-style-type: none"> - At 18 months - At 4 years (frequent doses is recommended) 	<ul style="list-style-type: none"> - At 18 months - At 4 years(DT) 		At 4-6 years
Reaction	Small papule which crust then disappear in 8-12 weeks leaving permanent scar.	<ul style="list-style-type: none"> No reaction; but values; - Low cost - Give both local & humoral immunity. - Virus excreted in stool → transmitted to others → community immunity. 	<ul style="list-style-type: none"> - Fever ,local tenderness - Irritability and crying for > 3 hours. - Shock like; hypotonic hyporesponsive episode - Convulsions - Encephalopathy. 	<ul style="list-style-type: none"> - Local reaction : pain tenderness, swelling & erythema. - Fever - Headache 	<ul style="list-style-type: none"> - Mild fever - Faint skin rash may occur 1-2 weeks after vaccination → last for 1-2 days.

Complications	BCG	Oral polio vaccine	DTaP	Hepatitis vaccine	MMR
	<ul style="list-style-type: none"> Regional (axillary) lymphadenitis ⇒ need INH Abscess formation Dissiminated infection if given to immunodef. Or improper attenuation ⇒ need anti- TB. Drugs. 	<ul style="list-style-type: none"> Failed vaccine due to <ul style="list-style-type: none"> - defect storage - vomiting or diarrhea Vaccine associated paralytic polio (incidence: 1 / 750.000) 	Severe previous reaction (usually due to pertussis vaccine)	<ul style="list-style-type: none"> Failed vaccine due to:- defect storage - injections in buttocks 	<ul style="list-style-type: none"> Encephalitis.
General contraindications and precautions ❖ Contraindications to all vaccines <ul style="list-style-type: none"> Serious allergic reaction (e.g., anaphylaxis) after a previous vaccine dose Serious allergic reaction (e.g., anaphylaxis) to a vaccine component ❖ Precautions: Moderate or severe acute illness with or without fever					
Additional contraindications <ul style="list-style-type: none"> Tuberculin +ve reactors Premature. 			See later	See later	See later
Other forms			Immunodeficient contacts <ul style="list-style-type: none"> In nurseries Inactivated polio vaccine (Salk): <ul style="list-style-type: none"> * Dose ⇒ 0.5 ml S.C. * Given if sabin vaccine is contraindicated * Dose of Salk before OPV reduce OPV associated paralysis by 90% 	TdaP and Td contain reduced dose diphtheria toxoid to be given as boosters to adolescents when pertussis vaccine is unnecessary	<i>ProQuad vaccine;</i> MMRV (contain varicella vaccine as well) licensed in children 1-12 years.

❖ **Contraindications to live virus vaccines**

- Immunosuppressed patient (immunosuppressive therapy or diseases ; acquired or congenital)
- Malignancy or current chemotherapy
- Pregnant mother or planned pregnancy within 28 days

Specific contraindications and precautions to commonly used vaccines

Vaccine	True contraindications and precautions
DTaP	<p>Contraindications</p> <ul style="list-style-type: none"> - Encephalopathy (e.g., coma, prolonged seizures) - Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, (Decision: defer DTaP until neurologic status stabilized) <p>Precautions</p> <ul style="list-style-type: none"> - Fever of $> 40.5^{\circ}\text{C} \leq 48$ hours after receiving a previous dose - Shock like state ≤ 48 hours after receiving a previous dose - Seizure ≤ 3 days of receiving a previous dose - Persistent crying lasting ≥ 3 hours ≤ 48 hours after receiving a previous dose
MMR	<p>Contraindications</p> <ul style="list-style-type: none"> - Known severe immunodeficiency (However the vaccine is allowed:- 1 month after cessation of high dose steroids, 3 months off chemotherapy and for HIV cases who are not severely immunosuppressed with CD4 percentages $\geq 15\%$ for ≥ 6 months) - Malignancy or current chemotherapy - Pregnancy or planned pregnancy within the next 28 days - Persons with anaphylactic egg or neomycin allergy <p>Precautions</p> <ul style="list-style-type: none"> - Recent (≤ 11 months) receipt of antibody-containing blood product - Thrombocytopenia
Hepatitis B	<p>Contraindication</p> <ul style="list-style-type: none"> - Pregnancy - Autoimmune disease (e.g. systemic lupus erythematosus) <p>Precautions</p> <ul style="list-style-type: none"> - Infant weighing $< 2,000$ grams

(Current Pediatrics textbook)

Other Vaccines (Non Compulsory in Egypt)

General indications: - High risk patients - Household contacts - Travelers to endemic areas

Vaccine	Nature	Dosage (0.5 ml)	Other indications /notes
Heamophilus influenza type B (HiB) vaccine^s	Antigenic part of the capsule	- IM - At 2,4,6 months - Booster dose at 15 mo.	* Routine immunization * Functional or anatomic asplenia * Immune compromised e.g Complement deficiency
13-valent pneumococcal conjugate vaccine (PCV13); <i>Prevnar</i>[*]	Capsular polysaccharide antigen of 13 pneumococcal serotypes	- IM	
Meningeococcal vaccines (MCV4 And MenB)	Purified capsular polysaccharide of types A, B, C, Y, W135	- SC (local erythema is a common side effect)	
Hepatitis A (<i>Havrix or Vaqta</i>)	Inactivated	- I.M.; 2 doses 6 months apart - Given above 1 year	Children with chronic hepatitis B or C infections or at high risk of their infections.
Typhoid vaccines			
1- Vi capsular vaccine	Conjugated vaccine	- I.M single dose - Given above 2 years	<u>Drawbacks:</u> * Short period of effectiveness * Fever , headache , malaise
2- TY 21a	Live attenuated	- Oral single dose.	
3- TAB vaccine	Heat phenol inactivated	- ¼ ml SC ; 2 doses 1 mo. apart	
Influenza vaccine^{**}	Inactivated viruses	- IM ;1 dose (2 doses 1 mo apart for children < 9 years who didn't get the vaccine before) - Dose for 6 mo to 3 years (0.25 ml) , Dose > 3 years :0.5 ml - Common type for season	* Chronic lung diseases * Patients on long term aspirin. * Annual shots for seasonal flu protection
Chicken pox vaccine	Live attenuated	- SC - Two doses: 3 months apart for children 12 months -12 years And 4 weeks apart for children ≥ 13 years.	* Routine immunization of children ≥ 12 months of age * Patients on long term aspirin * Post exposure prophylaxis if given within 3-5 days of exposure with efficacy of 95%

§ **Hib vaccine** is not generally recommended for children 5 years of age or older.

* **A 23-valent pneumococcal unconjugate polysaccharide Vaccine (Pneumovax23)**

- Its use in children is limited to those with certain chronic medical conditions not for routine immunization (e.g., heart disease or diabetes), immunocompromising conditions, cerebrospinal fluid leaks, or cochlear implants
- It does not produce a long-lasting immune response and does not reduce nasopharyngeal carriage.
- Licensed in children above 2 years

** **Influenza vaccine**

- May be complicated with self-limited fever, malaise or local reactions
- **Recent guidelines:** Children with only hives following exposure to egg can be vaccinated provided :

1. The inactivated influenza vaccine is used
2. Vaccination is by a health care provider experienced in recognizing and treating allergic reactions
3. The child is observed for 30 minutes following vaccination.

Children with more serious allergic reactions to egg, such as angioedema, respiratory symptoms, or anaphylaxis, may be eligible for inactivated influenza vaccine but after full assessment by an allergist for vaccine risk.

Rota virus vaccine (Rotarix)

- Live attenuated
- Given orally; 2.5 ml/dose
- Two doses 4 weeks apart
- The first dose must be before 5 months and final dose must be before **6 months**
- Efficacy: 70 %
- Complications: loose stool and low grade fever
- Avoided in gastro enteritis, immunodeficiency, anaphylaxis and beyond 6 months

Rabies vaccine

- After symptoms of infection develop, rabies is almost invariably fatal in humans
- Human rabies is preventable with appropriate and timely postexposure prophylaxis the immunity persists for 2 years or more.
- Two inactivated preparations are licensed in the United States.
 1. Imovax Rabies :Human diploid cell vaccine (HDCV)
 2. RabAvert :Purified chick embryo cell vaccine (PCEC)

Protocol:

- 1 mL is given intramuscularly on the day of exposure (day 0) and on days 3, 7, and 14 following exposure.
- Immune suppressed individuals should receive an additional dose on day 28
- Rabies Immunoglobulin (RIG) should also be given as soon as possible after exposure (20 IU/kg) ; most of the dose is infiltrated into and around the wound and the rest is given IM
- In previously vaccinated individuals—RIG should not be administered, and only two doses of vaccine on days 0 and 3 after exposure are needed

N.B: Vaccination in immunodeficient Children

- Congenitally immunodeficient children should not be immunized with live-virus vaccines (oral polio vaccine [OPV, available only in developing countries], rotavirus, MMR, VAR, MMRV, yellow fever) **or** live-bacteria vaccines (BCG or live typhoid fever vaccine).
- Depending on the nature of the immunodeficiency, other vaccines are safe, but may fail to evoke an immune response.
- Children with cancer and children receiving high-dose corticosteroids or other immunosuppressive agents should not be vaccinated with live-virus or live-bacteria vaccines.
- Live-virus vaccines may also be administered to previously healthy children receiving:
 1. Low to moderate doses of corticosteroids (defined as up to 2 mg/kg/day of prednisone or prednisone equivalent, with a 20 mg/day maximum) for less than 14 days
 2. Children without other immunodeficiency receiving short-acting alternate-day corticosteroids
 3. Children being maintained on physiologic corticosteroid therapy
 4. Children receiving only topical, inhaled, or intra-articular corticosteroids.



Neonatology

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الدفعة الـ 14

Neonatal Resuscitation

Introduction

- Resuscitation is the immediate steps performed to optimize newborn airway, breathing & circulation after birth
- A person skilled in basic neonatal resuscitation, whose primary responsibility is the newly born baby, should be present at every birth
- Completion of the Newborn Resuscitation Program (NRP) of the American Academy of Pediatrics/American Heart Association by every caregiver helps ensure a consistent approach to resuscitations and team-based training
- NRP Flow Diagram follow A-B-C (Airway-Breathing-Compressions) when other programs follow C-A-B (Compressions-Airway-Breathing) because the vast majority of newborns who require resuscitation have a healthy heart

Routine care of delivered baby

- Receive the baby in a pre-warmed towels
- Place the newborn on the warming table.
- Dry the infant completely and discard the wet linens; Ensure that the infant remains warm. Extremely small infants may require extra warming techniques such as wrapping the body and extremities in a plastic wrap or bag or the use of an exothermic mattress
- Place the infant with head in midline position, with slight neck extension
- Suction the mouth, oropharynx, and nares thoroughly with a suction bulb **if** there is obvious obstruction or the baby requires positive pressure ventilation.
- Quick evaluation of the infant by **Apgar scoring**
 - * At 1 minute → Reflects the need for resuscitation (????)
 - * At 5 minutes → Reflects adequacy of resuscitative efforts.
 - May predict the neurologic outcome

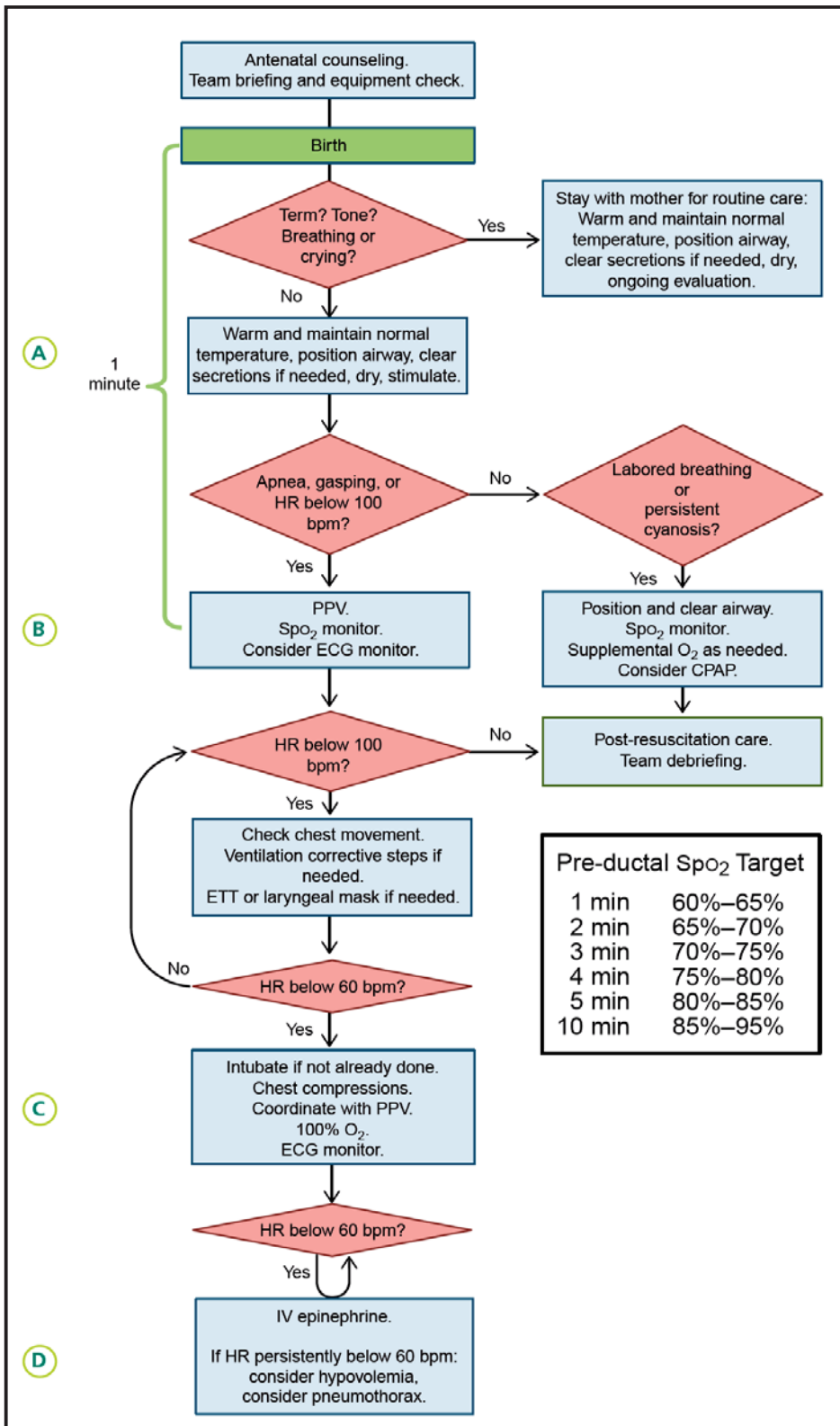
Sign	0	1	2
Color (Appearance)	Blue or pale	Pink with blue extremities.	Completely pink.
Heart rate (HR; Pulse)	Absent	Under 100 / min	over 100 / min
Response to nasal catheter (Grimace)	No response	Grimace	Cough, sneezing.
Muscle tone (Activity)	Limp (flaccid)	Some flexion	Well flexed
Respiration	Absent	Slow , irregular	Normal and crying

“Resuscitation if required, it should be initiated immediately after birth without delay or pending APGAR scoring at 1 minute” *Mohamed El Koumi*

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Sequence of intervention

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The NRP recommends that at the time of birth, the baby should be assessed by posing three basic questions:

1. Full term?
2. Good muscle tone?
3. Breathes spontaneously or crying?

1. If the answer to all questions are YES: Provide routine care:

- Dry the baby
- Provide warmth (wrapping)
- Position the head and neck to open the airway
- The infant should be placed on the maternal chest or abdomen
- The cord should not be clamped and divided until at least 30 to 60 seconds have passed.
- IM Vitamin K (if consented)
- Continue evaluation



2. If the answer to ANY of these questions is NO: The initial steps of resuscitation should start:

- Dry the baby
- Provide warmth (wrapping -warmer – plastic bags for preterm)
- Position the head and neck to open the airway
- Clear secretions if needed (mouth then nose)
- **Tactile stimulation** for compromised breathing by flicking of the soles of the feet or rubbing the back.



If breathing does not start after two attempts at tactile stimulation, the baby should be considered to be in secondary apnea, and respiratory support should be initiated

N.B: For those infants who require resuscitation beyond the initial steps because of inadequate or absent respiratory effort, the cord should be clamped and divided shortly after birth

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1. Apnea / Gasping?
Or
2. Heart rate <100 bpm?

1. NO → Breath spontaneously with HR >100 BUT labored breathing Or Cyanosis

- Position airway And Clear secretions if needed
- Attach pulse oximeter to right hand → Monitor SpO₂
- Supplemental oxygen as needed.

As a rule ; if oxygen is required during resuscitation → start with room air as the initial concentration for babies ≥ 35 weeks and 21% to 30% oxygen for babies < 35 weeks' gestation, increase gradually to keep SpO₂ lie within the minute-specific reference range advised by the NRP

- Consider CPAP
- Post resuscitation care (Indicated for all cases requiring resuscitation)

2. YES → There is Apnea or Gasping or HR < 100 bpm

- Call for help
- Ensure the baby is dry, warm and the airway is patent
- SpO₂ and ECG monitor
- **Provide positive pressure ventilation (PPV):**
 - Begin with an inspiratory pressure of **20- 25** cmH₂O at rate of **40-60** breath per second for **30** seconds
 - Using bag and face mask or T-piece resuscitator (Neopuff)

The most important indicator of successful PPV is a rising heart rate

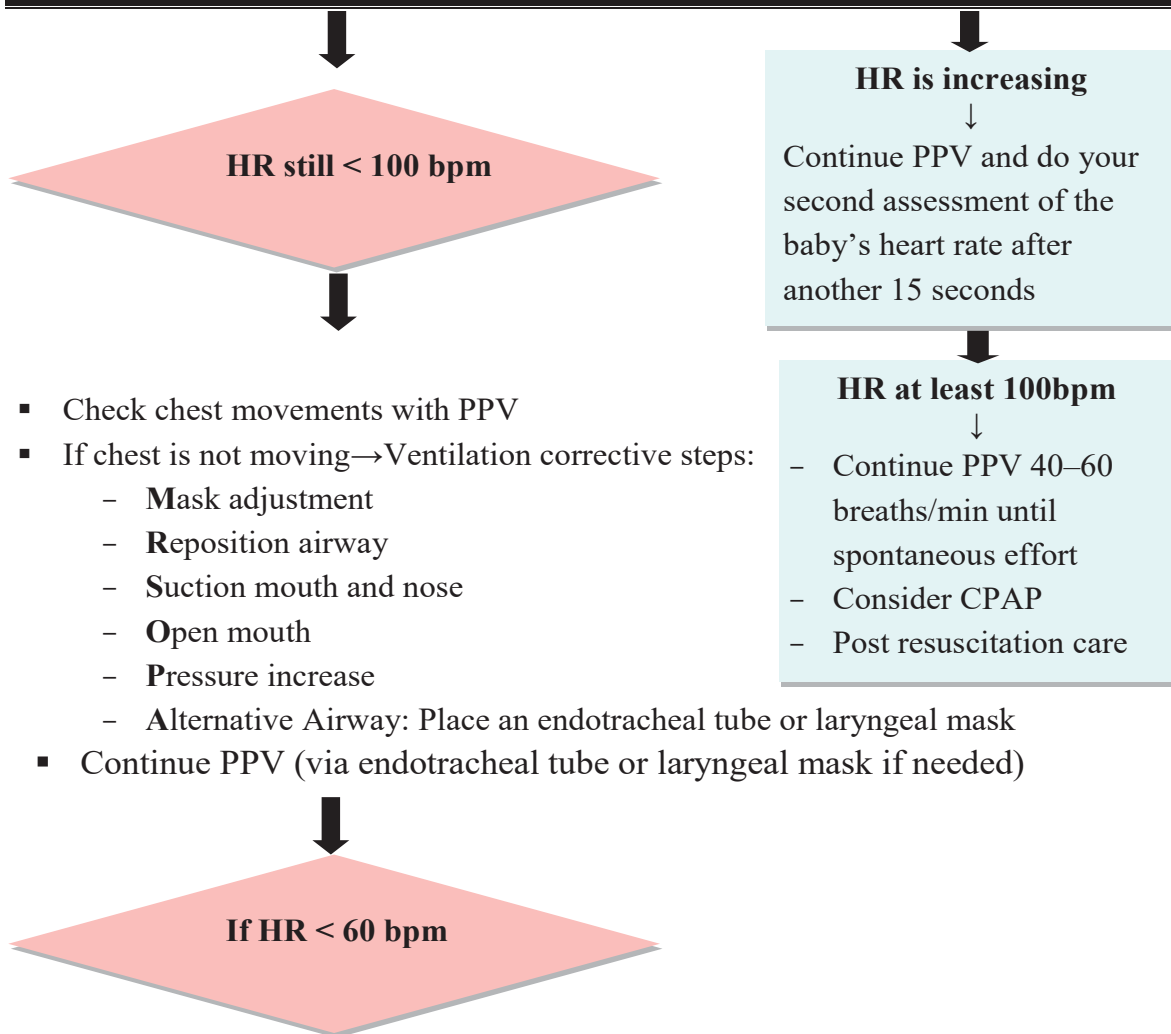


N.B: Indications for PPV:

1. Apnea or gasping
2. Heart rate < 100 bpm
3. Oxygen saturation below the target range despite free-flow oxygen or CPAP

When indicated, PPV should be started within 1 minute of birth

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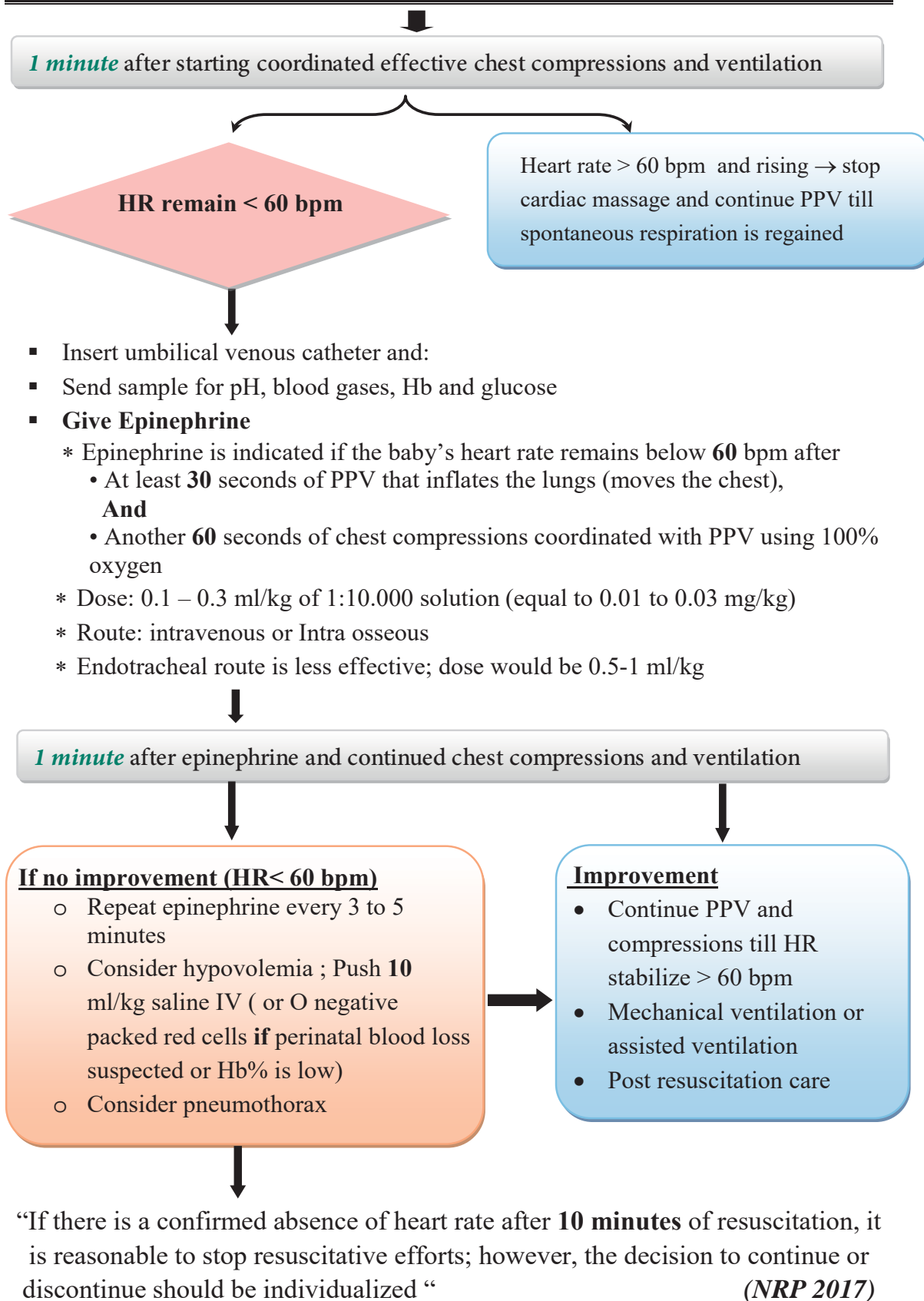


Start chest compressions:



- Indicated if the baby's HR remains < 60 bpm after at least 30 sec. of PPV that inflates the lungs as evidenced by chest movement with ventilation
- Depth of compressions is about 1/3 of the antero-posterior diameter of the chest
- The goal is to give 90 compressions per minute and 30 ventilations per minute (3 compressions and 1 ventilation every 2 seconds)
- Continue PPV via endotracheal tube with **100%** oxygen
- ECG monitor

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Post resuscitation care

Babies who required supplemental oxygen or PPV after delivery should:

- Be evaluated frequently during the immediate newborn period.
- They often require ongoing respiratory support, such as supplemental oxygen, nasal continuous positive airway pressure (CPAP), or mechanical ventilation and admission to nursery or NICU

Medical conditions may occur in babies who required resuscitation

Organ System	Management Considerations
Neurologic <ul style="list-style-type: none"> - Apnea - Seizures - Irritability - Poor tone - Poor feeding 	Monitor for apnea. Support ventilation as needed. Monitor glucose and electrolytes. Consider anticonvulsant therapy. Consider therapeutic hypothermia. Consider delayed initiation of feedings and use of intravenous fluids
Respiratory <ul style="list-style-type: none"> - Respiratory distress - Low oxygen saturation - Pneumothorax 	Maintain adequate oxygenation and ventilation. Consider antibiotics. Consider x-ray and blood gas. Consider surfactant therapy. Consider delayed initiation of feedings and use of intravenous fluids
Cardiovascular <ul style="list-style-type: none"> - Hypotension - Tachycardia 	Monitor blood pressure and heart rate. Consider volume replacement or inotrope administration if baby is hypotensive
Renal <ul style="list-style-type: none"> - Decreased urine output - Edema - Electrolyte abnormalities 	Monitor urine output. Monitor serum electrolytes as indicated. Monitor weight. Restrict fluids if baby has decreased urine output and vascular volume is adequate
Gastrointestinal <ul style="list-style-type: none"> - Feeding intolerance - Abnormal liver function tests - Gastrointestinal bleeding 	Consider abdominal x-ray. Consider delayed initiation of feedings and use of intravenous fluids. Consider parenteral nutrition
Metabolic <ul style="list-style-type: none"> - Metabolic acidosis - Hypoglycemia - Hypocalcemia - Hyponatremia - Hyperkalemia 	Monitor blood glucose. Monitor serum electrolytes as indicated. Consider intravenous fluids. Replace electrolytes as indicated
Hematologic <ul style="list-style-type: none"> - Anemia - Thrombocytopenia - Delayed clotting, 	Monitor hematocrit, platelets and coagulation studies as indicated
Hypothermia	Delay bathing.

(NRP 2017)

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Self-assessment questions by NRP**Question 1**

- A. A newborn is apneic. She does not improve with initial steps, and PPV is started. The first assessment of heart rate is 40 beats per minute. After 30 seconds of positive-pressure ventilation that moves the chest, her heart rate is 80 beats per minute. Chest compressions (should)/(should not) be started. Positive pressure ventilation (should)/(should not) continue
- B. A baby has received chest compressions and coordinated ventilation. You briefly stop compressions and the electronic cardiac (ECG) monitor shows the baby's heart rate is 80 beats per minute. You should (continue)/(stop) chest compressions. You should (continue)/(stop) positive-pressure ventilation
- C. Ventilation that moves the chest has been performed through an endotracheal tube for 30 seconds and continued with chest compressions and 100% oxygen for an additional 60 seconds. If the baby's heart rate remains below (60 beats per minute)/(80 beats per minute), you should give epinephrine while continuing chest compressions and ventilation
- D. In the absence of shock or a history of acute blood loss, routine administration of a volume expander (is)/(is not) recommended
- E. Your team is resuscitating a baby born at term. His heart rate is 40 beats per minute after ventilation through an endotracheal tube and coordinated chest compressions. You determine that epinephrine is indicated. Your team should (quickly attempt to place a peripheral intravenous catheter in his right hand)/(insert an umbilical venous catheter or an intraosseous needle).

Question 2

- A. You have turned on the radiant warmer in anticipation of the birth of a baby at 27 weeks' gestation. List 3 additional steps that will help maintain this baby's temperature.
- a. _____
- b. _____
- c. _____
- B. A baby is delivered at 30 weeks' gestation. At 5 minutes of age, she is breathing, has a heart rate of 140 beats per minute, and is receiving CPAP with 30% oxygen. An oximeter on her right hand is reading 95% and is increasing. You should (decrease the oxygen Concentration)/(begin positive-pressure ventilation).
- C. A baby is born at 26 weeks' gestation. The initial steps of care, including gentle stimulation, have been completed and he is nearly 1-minute old. He is not breathing and his heart rate is 80 beats per minute. You should (start CPAP with a face mask)/(start positive-pressure ventilation).

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Primitive Reflexes

Idea

- Primitive reflexes are automatic stereotypic movements directed from the brainstem and require no cortical involvement
- They are needed for survival and development in the early months of life
- As the higher cortical centers begin to mature → successive disappearance of these reflexes take place allowing proper neurological development

Moro (Startle) Reflex

- Present at birth and disappears by 5- 6 months of age
- Start to develop intrauterine at 32 weeks and fully mature at 37 weeks

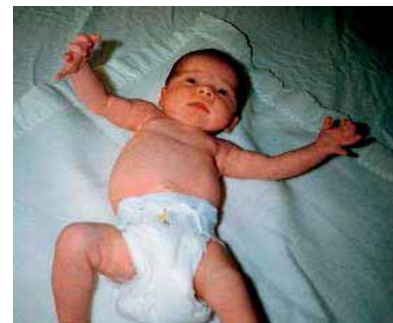
• Stimulus

- The head is gently lifted then released suddenly into examiner's hand (avoid in preterm & suspected intra cranial hemorrhage)
- Sudden withdrawal of the blankets from underneath the infant
- Making a loud noise near the ear



• Response

- Extension of the trunk
- Extension and abduction of the arms with "fanning" of the fingers followed by flexion and adduction "as if the infant embraces himself"
- Loud crying may follow





• Clinical value

- Normal reflex in the normal time frame → Normal neurodevelopment
- Abnormal reflex
 - Sluggish in sedated newborn and sepsis
 - Exaggerated in early kernicterus
 - Unilateral (asymmetrical) in Erb's palsy, fracture clavicle or humerus
- Absent reflex (two sided)
 - Premature < 28 weeks
 - CNS depression by e.g. Anoxia, anesthesia or intra cranial hemorrhage
- Reflex persisting beyond 6 months is seen in neurodevelopmental disorders e.g. cerebral palsy , autistic disorders

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Grasp Reflex

	Palmar grasp reflex	Solar grasp reflex
Present	From birth to 2 months	From birth to 10 months
Stimulus	 <p>Light touch to the palm</p>	 <p>Light touch to the sole</p>
Response	Grasp response	
Clinical value	<ul style="list-style-type: none"> • Normal reflex in the normal time frame → Normal newborn neurodevelopment • Help estimation of the gestational age; develops at 28 weeks and become fully mature by 32 weeks gestation • Absent in the same side of Klumpke's palsy 	

Stepping Reflex

- Present at birth and disappear by 6th week of age
- Stimulus: Hold the baby upright with his soles touching a flat surface
- Response: the baby starts walking movements



Placing Reflex

- Presents at birth and disappears by 6th week of age
- Stimulus: Hold the infant upright with one foot touching a surface of table and the dorsum of other foot touching the under edge of the table
- Response: The baby will flex then extend the leg to place it on upper surface of the table



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Rooting Reflex

- Present at birth and disappear by the 4th month of age
- Stimulus: Stroke the baby's cheek
- Response: The baby will turn towards the stimulus and open his mouth, usually looking for food
- Retained reflex in older children is associated with poor articulation and messy eaters



Spinal Galant Reflex

- Present at birth and disappear by 3-9 months of age
- Stimulus: lay the baby on his stomach and stroke along one side of his spine.
- Response: The baby will flex sideways toward the stimulated side
- Retained reflex in older children is associated with inability to sit still ('ants in the pants' child), and possible scoliosis



Asymmetric Tonic Neck Reflex (ATNR)

- Appear by the 1st month and disappear by the 6th months of age
- Stimulus: While in supine ,Turn the baby's head to one side
- Response: The baby will extend the arm and leg on this side while his other arm and leg will flex (fencer position)
- Clinical Value
 - It prepares the baby for future movements like turning from back to front and vice versa
 - Infant "stuck" in the fencing posture, is always abnormal and implies a CNS disorder
 - Retained reflex in older children is associated with possible scoliosis, and poor handwriting in childhood



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Landau Reflex

- Appear by the 3rd month and disappear by 24 months of age
- Stimulus: hold the baby in a prone (face down) position
- Response: The baby will extend head, trunk and limbs
- Clinical value:
 - A postural reflex that the infant needs to develop to sit and walk independently.
 - Absent in cerebral palsy



Parachute Reflex

- Present from 8-10 months and persist
- Stimulus: Hold the infant's trunk and then suddenly lower the infant as if he is falling.
- Response: The arms will spontaneously extend to brake the infant's fall, making
- Clinical value:
 - Protective reflex (a prerequisite to walking)



(Reference: Nelson Textbook 2016, Pediatric Neurology Seminars, 2010)

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Incubator care for critically ill neonate /very low birth weight

General care

- Temperature: 29-36 °C ;depending on birth weight ; core temp :36.5-37 c
- Humidity : 60 - 80% ; reduce insensible water loss
- Minimal handling and strict anti septic measures

Support Respiration

- Supply oxygen as needed by:
 - ✚ Ambient oxygen
 - ✚ Head box
 - ✚ Nasal catheter/Vapotherm
- Assisted ventilation: CPAP, BiPAP
- Mechanical ventilation
- Monitoring: pulse oximeter, Blood gases

Support Circulation

- Vascular access
- Intravenous fluids
- Transfusions : packed RBCs, fresh frozen plasma, albumin
- Inotropes e.g. Dopamine / dobutamine infusion
- Monitor :blood pressure, heart rate and capillary refill time



Support Nutrition

- Expressed breast milk or formula by nasogastric tube if enteral intake possible
- Total parenteral nutrition if enteral intake impossible(TPN consists of intravenous infusion of dextrose,amino acids , lipid, vitamins and minerals)

Specific treatment

- Phototherapy for jaundice
- Antibiotics for sepsis
- Anticonvulsants for seizures

Monitoring

- Vital data
- Fluid balance: Daily hydration state , weight, urine output, serum sodium
- Bloods: Blood glucose, electrolytes, CBC, CRP, sepsis workup...
- Drug levels and TPN follow up lab

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Birth Injuries

Cranial Injuries

1. Caput succedaneum

Subcutaneous fluid collection
Seen immediate after birth

Criteria



- Diffuse scalp swelling (cross the suture lines)
- Over the presenting part of the head
- Soft consistency
- May be with ecchymosis of the overlying skin

Treatment: Nothing required; it resolves in few days

2. Cephalhematoma

Sub-periosteal blood collection seen few hours after birth

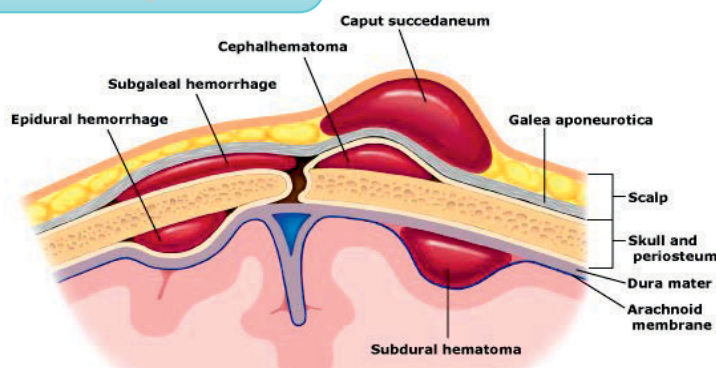
Criteria



- Localized scalp swelling (never cross sutures lines)
- Over any bone (commonly parietal or occipital)
- Firm consistency
- Possible associations:
 - Linear fracture in 15-20%
 - Anemia and jaundice (if large)

Treatment

- Observe ; most cephalhemaomas resolves spontaneously over 8 weeks
- Treat complications
 - Blood transfusion for anemia
 - Phototherapy for jaundice
 - Antibiotics, Incision and drainage for infection
- Avoid diagnostic aspiration→ carries risk of infection



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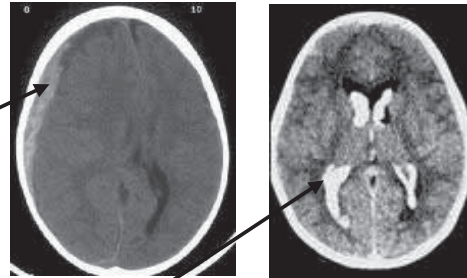
3. Intracranial Hemorrhage (ICH)

Risk factors

- Birth trauma
- Bleeding disorder
- Perinatal asphyxia (esp. in premature)

Types

- Subdural hemorrhage
- Subarachnoid hemorrhage
- Germinal matrix hemorrhage / intraventricular hemorrhage (GMH/IVH):
 - Mainly in preterm; mainly in the first 3 days of life
 - Starts in the highly vascular periventricular germinal matrix then may extend to the ventricular system.



Clinical picture

- Asymptomatic: Common; basically with GMH / IVH
- Mild hemorrhage
 - Reduced spontaneous movements
 - Hypotonia , poor suckling and Moro
 - Apneas
 - Anemia and fall of hematocrit
 - Abnormal eye movements
- Severe hemorrhage
 - Bulging fontanel
 - Decerebrate posturing
 - Hypotension, Collapse
 - Hypoxia
 - Seizures

Diagnosis

- Cranial CT scan or MRI
- Cranial ultrasonography:
 - Very sensitive & quick in diagnosing GMH/IVH
 - Infants <1,000 g are at highest risk and should undergo cranial ultrasonography within the 1st 3-7 days of age
- Coagulation profile (PT, PTT, platelets)
- CBC for anemia

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Prevention of IVH

- A single course of antenatal steroids for 24-34 wk pregnancies of gestation that are at risk for preterm delivery
- Low-dose indomethacin (0.1 mg/kg/day for 3 days) to VLBW preterm infants reduces the incidence of severe IVH
- Avoid fluctuation in cerebral blood flow by regulating blood pressure and PaCO₂
- Reduce infants fighting the ventilator by using synchronized ventilation and minimal handling and minimal ETT suctioning
- Correct any coagulopathy

Treatment

- Supportive care in NICU
- Treat anemia with blood transfusion
- Correct any coagulopathy
- Consider starting inotropes e.g. Dopamine if hypotension persists
- Symptomatic treatment for e.g. seizures, raised intracranial tension
- Repeat cranial ultrasound at intervals (usually within 3-5 days then weekly)
- Neuro Surgical consultation

Nerve Injuries

1. Facial nerve injury

Peripheral facial nerve injury results in paralysis of whole face on the same side:

- Inability to close the eye firmly
- Absent nasolabial fold.
- Asymmetric cry.
- Deviation of the mouth to healthy side



Treatment

- Care of the eyes with → eye drops & ointment.
- Care of feeding
- Physiotherapy → if persist more than 3 months → neuroplasty

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2. Brachial plexus injury

a. Duchenne-Erb's palsy

- Injury to the upper nerve roots (C₅, C₆) of brachial plexus
- Paralysis of upper arm muscles with loss of abduction, external rotation and supination

Criteria



Look: The arm is adducted, internally rotated and pronated (*Waiter's tip posture*)

Test: Lost Moro reflex, and preserved Grasp reflex on the affected side

Association: Phrenic nerve palsy in 75 % of cases

- Present with respiratory distress, and predominant thoracic breathing
- Diagnosed by :chest x ray (inspiration film) and fluoroscopy (detect paradoxical movement)

Treatment

- Partial intermittent immobilization in opposite position i.e. abduction, external rotation and supination (*Statue of liberty splint*)
- Physiotherapy after one week (after resolution of nerve edema) to prevent muscles contractures

Prognosis

- Full recovery occur in more than 90% by 3 months
- If no improvement within 3 months, consult neurosurgery

b. Klumpke's palsy

- Injury to the lower nerve roots (C₇, C₈, T₁) of brachial plexus
- Paralysis of all intrinsic muscles of the hand

Criteria



Look: Claw-hand deformity

Test : Lost Grasp reflex, and preserved Moro reflex on the affected side

Association: Horner syndrome if sympathetic fibers of T₁ are involved → ptosis, meiosis, enophthalmos and anhidrosis

Treatment

- Hand is kept in neutral position with pad of cotton in the fist (*hand writing position*)
- Physiotherapy

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Bone Injuries

Fracture clavicle

Commonest bone to be fractured in neonates especially if large and breech



Look:

- Bone irregularity and Crepitus on the affected side
- Pseudo paralysis of the affected limb
- May be excessively irritable newborn

Test: Moro reflex → Absent Moro on the affected side

Request: Chest X ray → diagnostic (soft tissue ultrasound has equal sensitivity and safer)

Treatment

- Decrease pain with analgesics
- The infant's sleeve may be pinned to the shirt to limit movement until the callus begins to form

Soft tissue Injuries

1. Liver or Spleen

- Clinical picture**
- Severe pallor → up to hypovolemic shock .
 - Indirect hyperbilirubinemia
 - Abdominal distension with discoloration of abdominal wall.
 - Abdominal ultrasound is diagnostic.(? paracentesis)

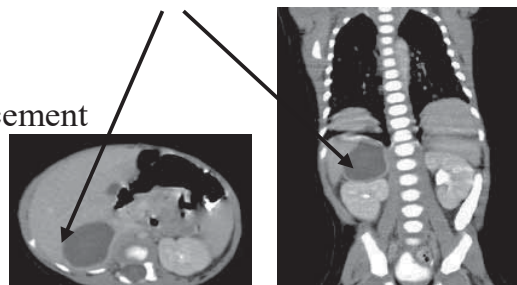
- Treatment**
- Blood transfusion.
 - Surgical exploration

2. Adrenal hemorrhage

- Risk factors**
- Neonate adrenals are large, friable, highly vascular .
 - Unilateral in 90%; mainly on the right side.

- Clinical picture**
- Pallor
 - Flank mass
 - Adrenal insufficiency: vomiting , poor feeding , shock .
 - Abdominal ultrasound /CT → diagnostic

- Treatment**
- Blood transfusion
 - Intravenous fluids
 - Corticosteroids replacement



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Self assessment case scenarios

Case 3

This newborn infant develops tachypnea with cyanosis. She improves somewhat on oxygen but has predominantly thoracic breathing movements, and the chest x-ray, which appears to have been taken inadvertently at expiration, seems normal.

A. The procedure most likely to provide a specific etiologic diagnosis is

1. Venous blood gas
2. CT scan of the head
3. Fluoroscopy of the chest
4. Bronchoalveolar lavage
5. Blood culture

B. What is the diagnosis?



Case 4

You are asked to review a baby on the postnatal wards 12 hours of age after a difficult breech delivery.

The baby was said to be fractious and is not feeding. As a part of sepsis screen chest X ray was carried out

What is the diagnosis?



Case 5

A term 3.5 kg female baby at 34 hour of life was admitted for unexplained pallor and abdominal distension, she was born to 29 years old mother by difficult breech vaginal delivery and she had poor Apgar score at birth. On examination she was very pale, jaundiced, tachycardic and tachypneic. Abdominal examination revealed a smooth non tender mass in the right flank with no evidence of free fluid. Hb% was 6.8gm/dl, indirect bilirubin 14 mg/dl, PT >30 seconds, PTT >60 seconds. Urea, creatinine and liver enzymes were normal

- a. What is the expected diagnosis?
- b. What is the investigation of choice?
- c. What are the 4 main initial lines of treatment?

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Neonatal Septicemia

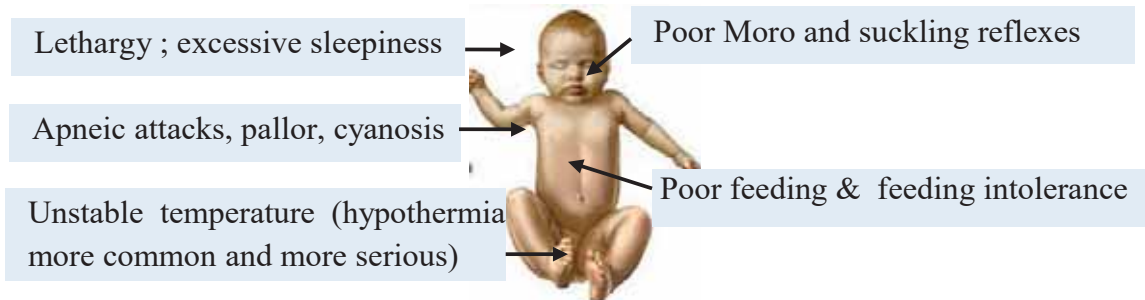
Definition: Serious systemic infection of the newborn.

Classification

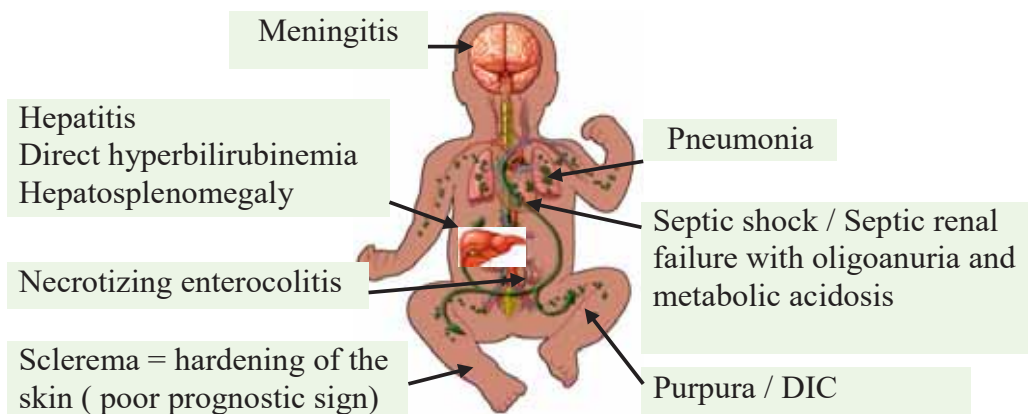
	Early sepsis	Late and nosocomial sepsis
Pattern	Acquired before or during delivery (vertical mother-to-child transmission)	Develop after delivery from organisms acquired in the hospital or the community
Onset	In the 1 st week (usually <72 hr)	After the 1 st week
Risk factors	<ul style="list-style-type: none"> • Prematurity • Premature rupture of membranes > 18 hr. • Chorioamnionitis • Maternal intrapartum fever $\geq 38.0^{\circ}\text{C}$ • Maternal bacteruria. 	<ul style="list-style-type: none"> • Prematurity. • Hospitalization • Umbilical catheterization , or poor cord care • Endotracheal intubation • Mechanical ventilation.
Organisms	<ul style="list-style-type: none"> • Group B streptococci (GBS) • E.Coli • Listeria monocytogenes 	<ul style="list-style-type: none"> • Staphylococcus Aureus. • Hemophilus influenza • Klebsiella. • Pseudomonas. • Viral or candida

Clinical picture

1. Early manifestations \Rightarrow Non specific = Not doing well baby



2. Late manifestations \Rightarrow Early manifestations plus more focal infections



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3. Presence: of one or more risk factors especially in premature or mechanically ventilated baby with persistent metabolic acidosis should suspect sepsis until prove otherwise. (Antibiotics must be used till negative cultures are obtained).

Diagnosis

1. History : for risk factors

2. Clinical picture

3. Investigations

a. Sepsis screen: Septicemia is suggested when:

CBC findings

- Leucopenia $< 5000/\text{mm}^3$ (with severe sepsis)
- Toxic granulations in neutrophils.
- Bandemia: Band cells (immature) $>20\%$ of total neutrophil count.
- Less commonly leucocytosis ($> 30.000 / \text{mm}^3$)
- Thrombocytopenia

Markers of inflammation

- Serial determination of C-reactive protein (CRP)
- ESR

b. Detect causative organism by

- Cultures of Blood, CSF, urine, and endotracheal aspirate.

c. Evidence of Multiorgan System Disease

- 1- Pulmonary: Chest x ray for pneumonia, blood gases
- 2- CSF analysis, culture and gram stain for meningitis
- 3- Liver enzymes, bilirubin, ammonia, prothrombin time, PTT
- 4- Serum urea and electrolytes, blood glucose

Differential diagnosis

Other causes of critically ill neonate: THE MIS FITS

- | | |
|---|--|
| T | : Trauma e.g. intracranial hemorrhage |
| H | : Heart disease e.g. congenital, hypoxic, hypovolemic |
| E | : Endocrine e.g. congenital adrenal hyperplasia |
| M | : Metabolic disturbances e.g. hypoglycemia, hypocalcemia |
| I | : Inborn errors of metabolism |
| S | : Sepsis |
| F | : Fits (seizures) |
| I | : Intestinal catastrophes e.g. intestinal obstruction, NEC |
| T | : Toxins |
| S | : Severe asphyxia |

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Management

A. Prophylaxis

Maternal intrapartum ampicillin prevent perinatal transmission of GBS

Indications

- Previous infant with invasive GBS disease
- GBS bacteruria during current pregnancy
- Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)
- Unknown GBS status at the onset of labor and any of the following:
 - Delivery at <37 weeks' gestation
 - Amniotic membrane rupture ≥ 18 hr
 - Intrapartum temperature $\geq 38.0^{\circ}\text{C}$

B. Curative

1. Incubator care in neonatal intensive care unit (NICU)

(See before)

2. Specific treatment

- Immediate parenteral antibiotics are initiated after taking appropriate cultures.
 - Antibiotics are given according to culture and sensitivity(C/S)
 - While waiting for C/S ; empiric antibiotic combinations is given:
 - For early onset sepsis: Ampicillin plus Gentamicin
 - For late onset sepsis: Vancomycin(or oxacillin) plus Gentamicin
 - Some experts recommend antifungal prophylaxis with fluconazole for particularly high-risk newborns—that is, those of extremely LBW (<1000 g) and low gestational age (<27 wk).
 - Third-generation cephalosporins such as cefotaxime or ceftazidime are valuable additions for treating documented neonatal sepsis and meningitis
- All antibiotics should be given for **10-14 days (3weeks for meningitis)**.
 - Dose and interval of antibiotics depends on birth weight and gestational age
 - Peak and trough levels of Gentamicin and Vancomycin are useful to ensure therapeutic levels and minimize toxicity

3. Treatment of complications

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Necrotizing Enterocolitis (NEC)

Definition

Syndrome of acute intestinal necrosis of unknown cause usually affects sick prematures with high mortality rate.

Risk factors

1. Prematurity

- The most important risk factor
- NEC affects 10% of infants < 1500 gm

2. Intestinal ischaemia due to

- Perinatal asphyxia
- Patent ductus arteriosus and indomethacin
- Polycythaemia
- Umbilical catheterization

3. Feeding

- Non breast feeding with hyperosmolar formula
- Aggressive enteral feeding in prematures



Pathogenesis

- Sloughing and necrosis of the intestinal mucosa especially at terminal ileum and proximal colon
- Superadded infection (Klebsiella, E-coli, Clostridia, & Viruses) ⇒ Gas formation within the bowel wall → extensive bowel necrosis and Septicemia → perforation & peritonitis



- Platelet activating factor, tumor necrosis factor and cytokines may play role

Clinical picture

Presentation is usually within 1st 2 weeks of life

A. Nonspecific Systemic signs: any combination of the following

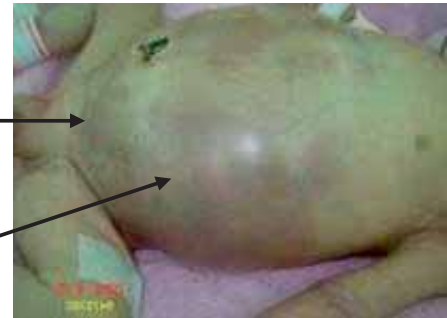
- Apnea
- Lethargy
- Decreased peripheral perfusion
- Shock (in advanced stages)
- Cardiovascular collapse
- Bleeding diathesis (consumption coagulopathy)



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B. Abdominal manifestations

- Feeding intolerance
- Delayed gastric emptying
- Abdominal distention (↑abdominal girth)
- Abdominal tenderness
- Ileus/decreased bowel sounds
- Abdominal wall erythema (advanced stages)
- Hematochezia

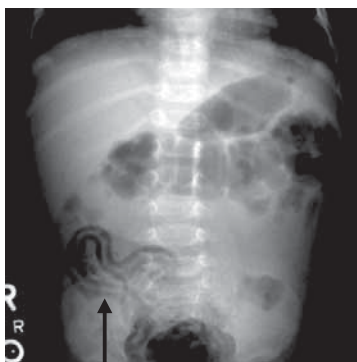


Investigations

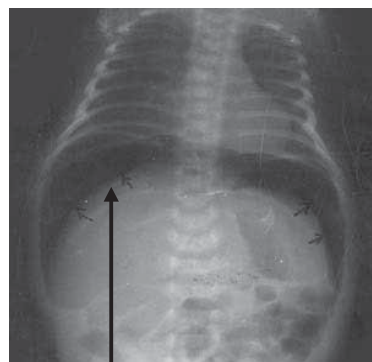
A. Radiological

1. X-ray abdomen

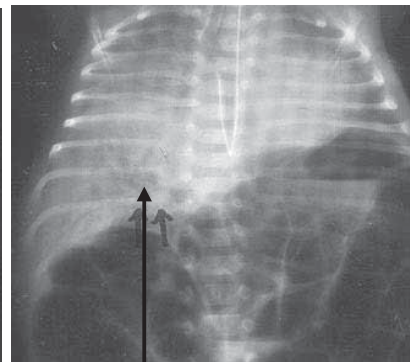
- View: Antero posterior and lateral
- Should be done and repeated every 8 hours in the first 2 days
- Findings



Pneumatosis-intestinalis
(gas in the intestinal wall)



Pneumo-peritoneum (gas
under the diaphragm) if
perforation occurred



Intrahepatic portal venous
gas

2. Abdominal ultrasound

- Sensitive for pneumatosis-intestinalis but require skilled sonographer
- Doppler of the splanchnic arteries can distinguish very early NEC from benign feeding intolerance in a mildly symptomatic baby

B. Laboratory findings

- Triad of thrombocytopenia, hyponatremia and metabolic acidosis.
- Stool examination for occult blood (Gaujac test).
- Sepsis workup: CBC, CRP and Culture of blood, stool, and CSF

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Sequalae of NEC

- GI sequelae include strictures, enteric fistulas, short bowel syndrome, malabsorption and chronic diarrhea
- Survivors of NEC have significantly impaired motor and cognitive outcomes

Prevention: Best evidence exist only for

- Induction of prenatal GI maturation with prenatal corticosteroids
- Standardized enteral feeding guidelines (Avoid aggressive feeding in preterm)
- Exclusive use of human milk.
- Avoidance of acid blockade
- Minimization of empiric antibiotic exposure.

Enterally fed probiotics→ controversial (cannot be universally recommended)

Treatment

Admit	<ul style="list-style-type: none"> ○ To NICU for full monitoring and supportive care
Stop	<ul style="list-style-type: none"> • Enteral feedings for 7-14 days according to severity
Start	<ul style="list-style-type: none"> ○ GIT rest and nasogastric decompression ○ Intravenous fluids / Total Parenteral Nutrition (TPN) ○ Broad-spectrum antibiotics for 10-14 days ○ Typical combination include: <ul style="list-style-type: none"> – Ampicillin /Gentamicin / Metronidazole. <i>Alternatively</i> treatments include: <ul style="list-style-type: none"> – Clindamycin, piperacillin-tazobactam, or meropenem, sometimes in combination with vancomycin.
Support	<ul style="list-style-type: none"> • For respiratory failure (oxygen therapy, ventilation) • For cardiovascular failure(fluid resuscitation, pressors)
Consult	<ul style="list-style-type: none"> ○ Pediatric surgeon at the earliest suspicion of developing NEC

(Manual of neonatal care 2017)

Congenital Infections (TORCH)

Etiology

Toxoplasmosis	Congenital Rubella	Cytomegalovirus	Herpes simplex type II
Toxoplasma gondii protozoan inhabit cats' gut → oocytes in their stool → contaminate food, water & in raw meat of infected cattle	Maternal German measles specially in the 1 st trimester	DNA virus infection can be: <ul style="list-style-type: none"> ○ Transplacental. ○ Perinatal ○ In breast milk 	DNA virus infection can be : <ul style="list-style-type: none"> ○ Transplacental ○ Contact with genital lesions during vaginal delivery → common

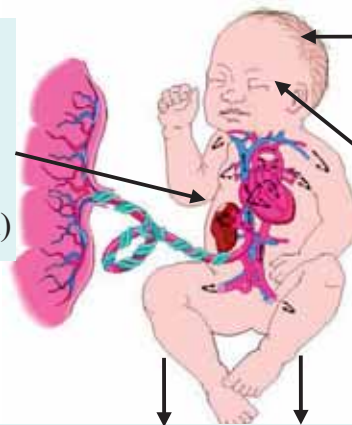
General clinical features

A. History suggestive of congenital infection

- Previous abortions or intra uterine fetal death
- Maternal Fever ,Skin rash or Skin vesicles during pregnancy

B. General features suggesting congenital infection : may be

- Hepatosplenomegaly
- Generalized lymphadenopathy.
- Anemia
- Thrombocytopenic purpura.
- Hepatitis (↑conjugated bilirubin)



- Mental retardation
- Seizures
- Microcephaly
- Chorioretinitis

- Low birth weight
 - Intra uterine growth restriction
 - Prematurity

General workup

- Detection of specific IgM or rising titer of specific IgG
- For clinical features e.g.
 - CBC with differential WBCs count
 - Fundus examination
 - Liver enzymes and bilirubin
 - Plain skull radiograph, CT, MRI
- Isolation of the causative organism

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Congenital Toxoplasmosis

Clinical picture

- General features
- Hydrocephalus /Microphthalmia /Chorioretinitis

Diagnosis

- General workup
- Isolate of the organism from the blood
- Skull X-ray, CT: Diffuse calcifications

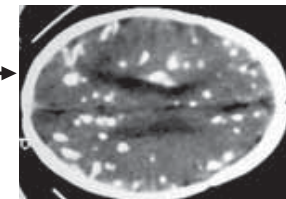
Treatment

A. Prevention

- Food hygiene
- Spiramycin for seropositive pregnant

B. Curative

- Symptomatic treatment
- Triple therapy for up to 1 year pyrimethamine ,folonic acid, sulphadiazine



Congenital Rubella Syndrome(CRS)

Clinical picture

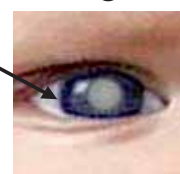
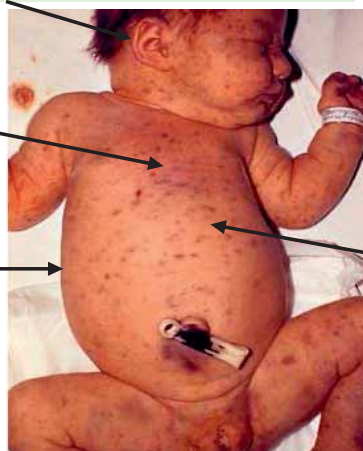
- Even if asymptomatic infection occurs in the mother, rubella can be transmitted across the placenta to the developing fetus.
- The earlier in gestation the infection occurs, the greater the injury
- 40% of fetuses infected during the first 8 weeks spontaneously abort
- Some infants at risk are normal
- Some appear normal at birth but later are found to have hearing loss
- Some are small for gestational age and at birth have congenital anomalies :

- Cataract, glaucoma, microphthalmia
- Sensorineural deafness , Meningoencephalitis

Congenital heart disease

- PDA
- Pulmonary stenosis

- Hepatosplenomegaly
- Lymphadenopathy
- Anemia
- Purpura
- Hepatitis



Chorioretinitis
(salt and pepper appearance)

In some cases a rubelliform rash or a characteristic raised, bluish, papular eruption, termed a blueberry muffin rash, may be evident as the result of dermal erythropoiesis

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Prognosis

Survivors of rubella syndrome are highly likely to be deaf and have significant psychomotor retardation

Diagnosis

- General workup
- Viral culture and specific IgM titers

Treatment

- Infants with congenital rubella are chronically infected and tend to shed live virus in urine, stools, and respiratory secretions for up to a year. Hence, they should be isolated when in the hospital and kept away from susceptible pregnant women when sent home
- Symptomatic treatment

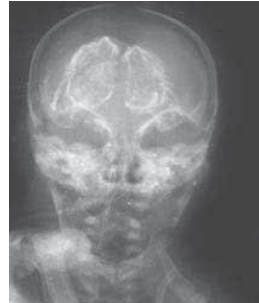
Prevention

- Rubella or MMR vaccine
- Pregnant exposed to German measles → abortion or I.V Immunoglobulin

Congenital CMV Infection

The commonest congenital viral infection (0.5–1 per 1000 live births)

- General clinical features and general workup as before
- Isolate the virus from urine
- Periventricular calcifications

**Treatment**

- Hyperimmune anti-CMV immunoglobulin.
- Symptomatic treatment
- Ganciclovir
- Avoided by blood products screening

Congenital HSV Infection

- Skin and mouth vesicles and ulcers
- Kerato conjunctivitis
- Encephalitis
- Disseminated form: (multi organ) ⇒ septic shock like

**Diagnosis**

- Isolate CMV from the vesicles or conjunctiva smears
- Skull X-ray, CT: May show diffuse calcifications
- Avoided by cesarean section for mothers with genital lesions and Acyclovir

Treatment: Symptomatic treatment + Acyclovir or Vidarabine

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Other Congenital Infections

Parvo B19

Parvo virus B19 is a small, non-enveloped, single-stranded DNA virus that causes erythema infectiosum (fifth disease) in children,

Clinical picture

Usually the fetus is unaffected

- May cause severe fetal anemia causing fetal hydrops (edema and ascites); implicated in approximately 10% of cases of fetal nonimmune hydrops
- Pathogenic sequence is as follows: maternal primary infection → trans placental transfer of B19 virus → infection of red blood cell precursors → arrested red blood cell production → severe anemia (Hb < 8 g/dL) → congestive heart failure → edema
- Anemia in the fetus is monitored by middle cerebral artery velocity waveform on Doppler ultrasound and treating with intrauterine transfusion, if necessary
- May cause fetal myocarditis/hepatitis
- If the baby survives; no long term residuals

Varicella zoster virus infection

- Congenital varicella syndrome:
 - Rare; 1-2% after maternal infection acquired in the first 20 weeks of gestation
 - May be limb hypoplasia, skin scars, microcephaly, cataract
- Perinatal infection within 5 days before to 2 days after delivery can cause fatal varicella in the infant. Treatment for perinatal infection:
 - Zoster immunoglobulin or IVIG
 - If clinical varicella developed, treat with IV acyclovir

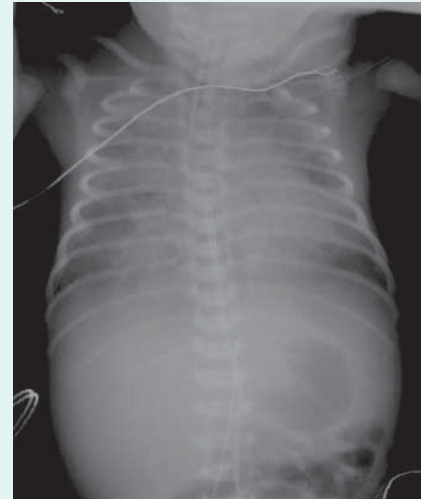
Self-assessment case scenarios

Case 6

This is a 3.2 kg term newborn female delivered via normal spontaneous vaginal delivery. Rupture of membranes occurred 21 hours prior to delivery with clear fluid. There was a maternal fever 38.1°C. Apgar scores were 8 and 9. The infant appears slightly pale and mottled, with persistent grunting, shallow respirations, and lethargy. Her fontanelles and Heart exam were normal.

Chest x ray is shown

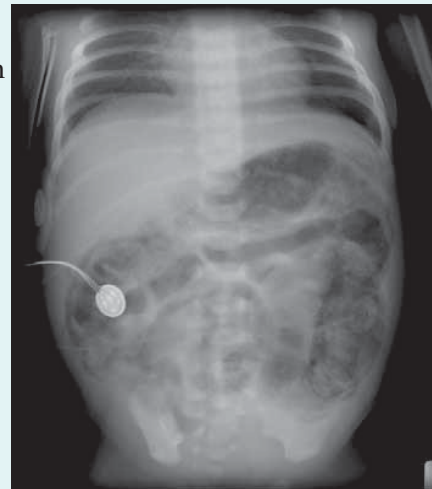
- What is the likely diagnosis?
- Comment on the X ray ?
- What are further investigations required ?



Case 7

A 28 weeks gestation infant has been born and has needed relatively little ventilator support. Feeds are introduced on day 3 and increased slowly. On day 5 he deteriorates and there was obvious abdominal distension. An abdominal X ray is obtained

- What does the x ray show?
- What do you think has happened?
- What will you do next?



Case 8

A baby boy delivered at 38 weeks' gestation with a birth weight of 2 kg and a head circumference of 31 cm. At day 3 postnatal, he had neonatal thrombocytopenia requiring platelet transfusion. Later, brainstem evoked responses indicated severe bilateral sensorineural deafness. His mother had a contact at 9 weeks' gestation with a family member with rash, and she developed same illness 1 week later.

- What is the diagnosis?
- What is the skin lesion seen?



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Neonatal Jaundice

- Jaundice: is yellowish discoloration of skin and mucus membranes due to increased serum bilirubin above normal levels
- Normal cord bilirubin is less than 3 mg/dl.
- Jaundice is obvious clinically in neonate when serum bilirubin exceeds 5 mg/dl

Bilirubin Metabolism

1. Production: Bilirubin is produced mainly from old RBCs

- Old RBCs give rise to globin and haem
- Globin enter the amino acid pool of the body
- Haem spilt into iron and biliverdin which change into unconjugated bilirubin
- Unconjugated (indirect) bilirubin has 3 criteria:
 - Fat soluble → can cross Blood Brain Barrier (BBB)
 - Water insoluble → can not be excreted in urine
 - Detected by indirect Van Den Berg reaction

2. Transport

Indirect bilirubin is carried on albumin
(unconjugated or hemebilirubin)

3. Uptake by hepatocytes

Bilirubin bind to cytoplasmic ligandins
; Z & Y proteins to deliver it to endoplasmic
reticulum where conjugation occur.

4. Conjugation

Conjugation of bilirubin stimulated by
glucoronyl transferase enzyme give rise to
conjugated or cholebilirubin which is
water soluble (excretable in urine) and lipid
insoluble (cannot cross BBB)

5. Secretion

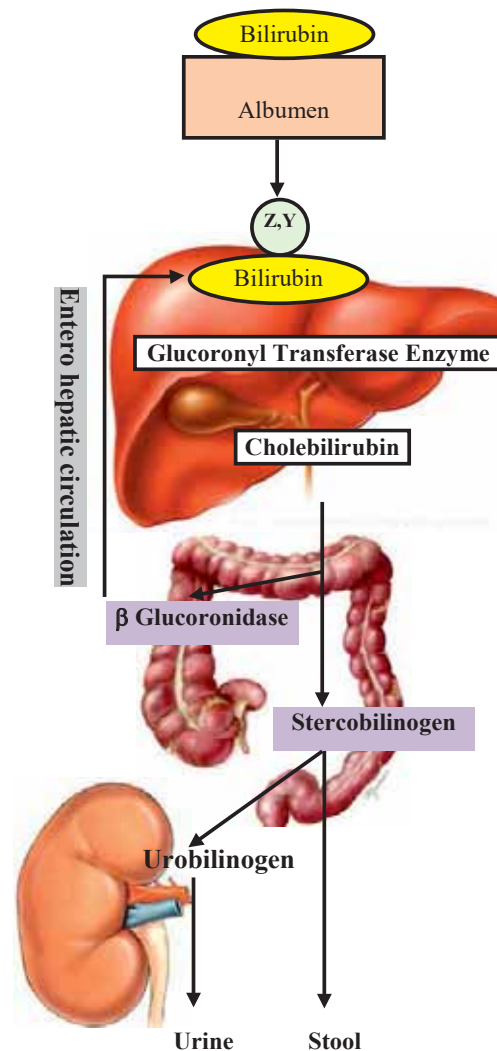
Active secretion of conjugated bilirubin by
liver cells into bile canaliculi.

6. Excretion

Excretion of conjugated bilirubin &
bile salts into the intestine.

7. Bilirubin in intestine

- Some amount is deconjugated by mucosal
enzyme; β glucuronidase →
unconjugated bilirubin → reabsorbed
to the liver (entero- hepatic circulation)
- Some amount is changed to
stercobilinogen → stool
- Small amount of stercobilinogen reach
the systemic blood (urobilinogen) → urine.



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Unconjugated Hyperbilirubinemia

High Total Serum Bilirubin (TSB) & conjugated bilirubin < 15 % of TSB

Causes

1. Bilirubin over production

I. Increased rate of hemolysis (Reticulocyte count elevated).

- a- Direct Coomb's test positive
 - Rh. incompatibility.
 - ABO blood group incompatibility
- b- Direct Coomb's test negative
 - Spherocytosis
 - α Thalassemia
 - Glucose-6-phosphate dehydrogenase deficiency.

II. Non hemolytic causes (normal reticulocyte count.)

- Extra vascular hemorrhage : Cephalhematoma & Internal hemorrhage
- Elevated RBCs load (Polycythemia) \rightarrow \uparrow RBCs turnover
- Enhanced enterohepatic circulation of bilirubin 2^{ry} to gastro intestinal stasis e.g. congenital pyloric stenosis and breast feeding jaundice

2. Defective uptake: Due to defective ligandins (Z&Y proteins)

3. Defective conjugation: Glucoronyl transferase enzyme may be:

- Absent \rightarrow Crigler – Najjar syndrome type I
- Deficient \rightarrow Crigler – Najjar syndrome type II
 \rightarrow Gilbert syndrome
- Immature \rightarrow Physiologic jaundice
- Under stimulated \rightarrow Hypothyroidism, hypoglycemia, hypoxia
- Inhibited \rightarrow Breast milk jaundice, Lucy- Driscoll syndrome

Clinical features

- Skin and sclera: bright yellow / orange
- Color of urine: usually normal.
- Color of stool : may be dark
- Possible Concurrent problems:
(Absent in physiologic jaundice)
 - * Risk of kernicterus if indirect bilirubin exceeds the binding sites on albumin or with leaky blood brain barrier
 - * Risk of anemia: if hemolysis exists



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• Timing of Clinical jaundice:

* In the 1 st day of life	- Hemolytic disease of newborn (Rh <u>or</u> ABO incompatibility (<i>until prove otherwise</i>)).
* In the 2 nd - 3 rd day of life	- Physiologic jaundice - Crigglar Najjar syndrome - Hemolytic anemia
* By the 4 th - 7 th days	- Physiologic jaundice in premature - Hemolytic anemia
* After the 1 st week	- Breast milk jaundice - Hemolytic anemia
* Persistent > 3 rd week	- Crigglar-Najjar syndrome - Physiologic jaundice in hypothyroid infant

Physiologic Jaundice

Incidence

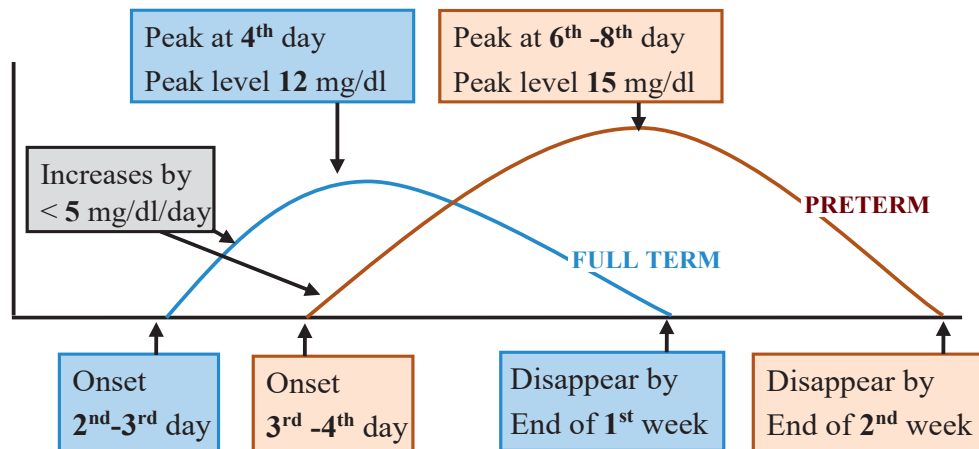
- Affects 40-50% of full term and 60% of preterm

Etiology

- Transient glucuronyl transferase enzyme immaturity .
- Metabolism of extra hemoglobin formed intrauterine
- Shorter life span of neonatal RBC's
- Reduced Z & Y proteins (Ligandins) during the 1st week

Characters

- Unconjugated hyperbilirubinemia (Direct bilirubin <1mg/dl)



- No pallor, organomegaly nor risk of kernicterus
- Diagnosed by exclusion (Well baby, No hemolysis, nor anemia)

Treatment

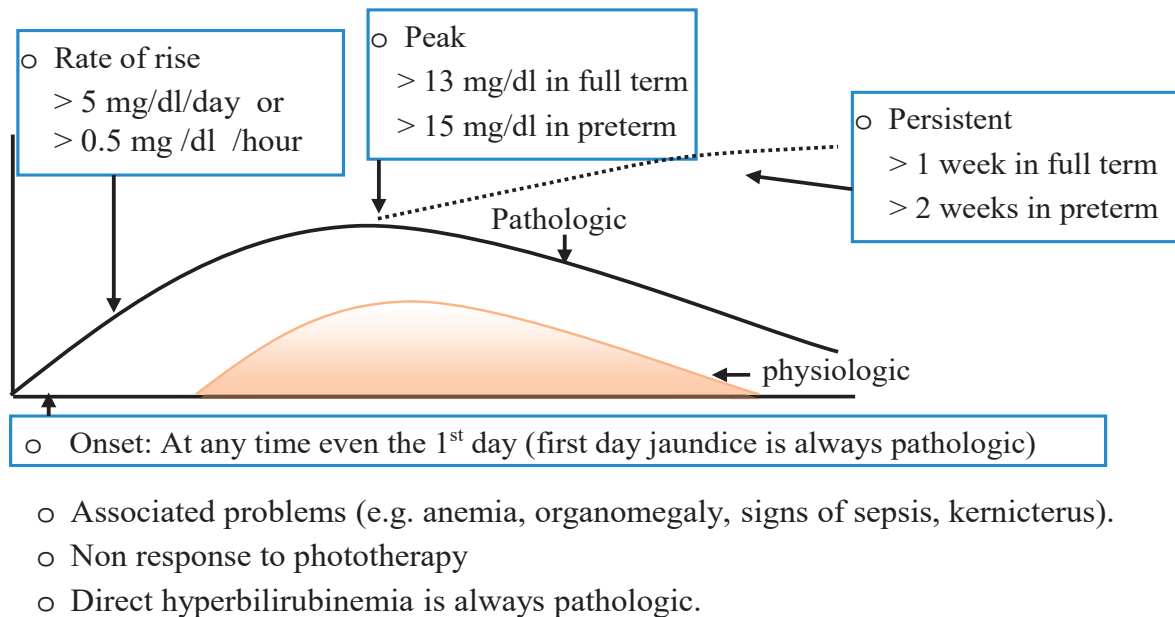
- Usually need no treatment; especially in full term
- Phototherapy or even exchange may be needed for VLBW

Differential diagnosis: From pathological jaundice

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Criteria of pathological jaundice

Jaundice is considered pathologic if the time of appearance, duration, or pattern varies significantly from physiologic jaundice or if the course is compatible with physiologic jaundice but the infant has other risk factors predisposing him to neurotoxicity :

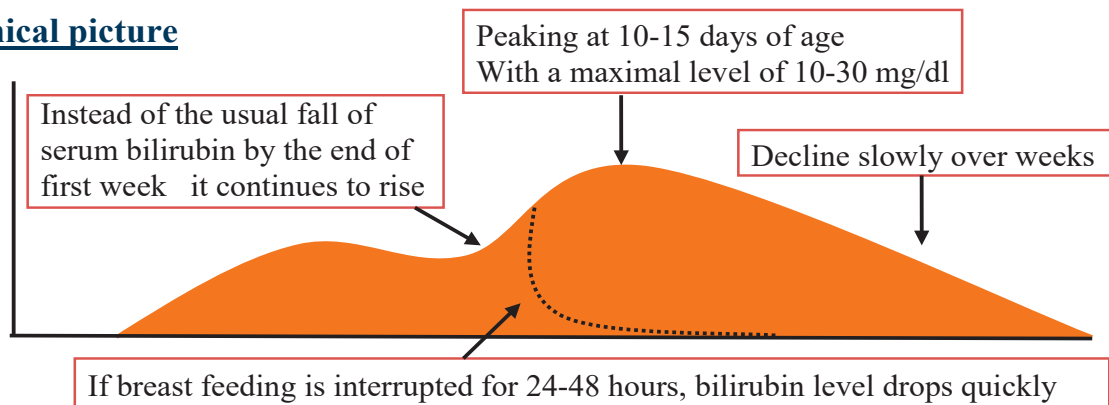


Breast Milk Jaundice

Incidence

- Affects 2-4 % of adequately breast fed, healthy full term.
- Recurrence rate 70% in subsequent pregnancies

Clinical picture



Etiology

Unknown ; Breast milk may contain:

- Pregnanediol → inhibit glucuronyl transferase enzyme.
- β glucuronidase → enhance entero hepatic circulation of bilirubin

Diagnosis

- By Exclusion (Normal liver functions & CBC) + Therapeutic trial

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Gilbert Disease

Etiology

- Autosomal dominant disorder.
- Decreased hepatic glucuronyl transferase level. (was thought to be due to deficiency of Z & Y proteins)

Clinical picture

- Mild hyperbilirubinemia, usually need no treatment

Crigler-Najjar Syndrome Type I

Etiology

- Autosomal recessive disorder.
- Absent glucuronyl-transferase enzyme

Clinical picture

- Severe disease; very high level of indirect bilirubin
- Unresponsive to phenobarbitone

Diagnosis

- Clinical picture
- Enzyme assay in liver biopsy

Crigler-Najjar Syndrome Type II

Etiology

- Autosomal dominant disorder.
- Partial deficiency of glucuronyl-transferase enzyme

Clinical picture

- Less severe than type I
- Responsive to phenobarbitone trial

Investigations of indirect hyperbilirubinemia

- 1- Total Serum Bilirubin (TSB) & direct fraction (direct fraction < 15 % of total)
- 2- Direct Coomb's test:
 - If positive → check blood group of infant & mother.
- 3- Hb/Htc value:
 - If high (Htc > 65%) → polycythemia.
 - If normal or low (Hb < 13gm/dl) → check Retic count
- 4- Reticulocyte count:
 - Normal → extravascular hemorrhage.
 - High (> 6%) → Check blood smear & osmotic fragility → G6PD enzyme assay.
- 5- Others
 - Check albumin if TSB is approaching the exchange level
 - Serum T₄ & TSH to rule out hypothyroidism if jaundice is prolonged
 - Phenobarbitone trial for Crigler-Najjar type II.
- 6- For a risk factor:
 - Sepsis screen If history and/or presentation suggest sepsis
 - Cranial ultrasound /CT for cephalhematoma

Hb = hemoglobin, Htc = hematocrit value, retics = reticulocytic count

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Treatment of indirect hyperbilirubinemia

Goals of therapy:

- Prevent neurotoxicity related to indirect-reacting bilirubin regardless of the cause
- Keep the maximal total serum bilirubin below pathologic levels by phototherapy and, if it is unsuccessful, by exchange transfusion

1. Phototherapy

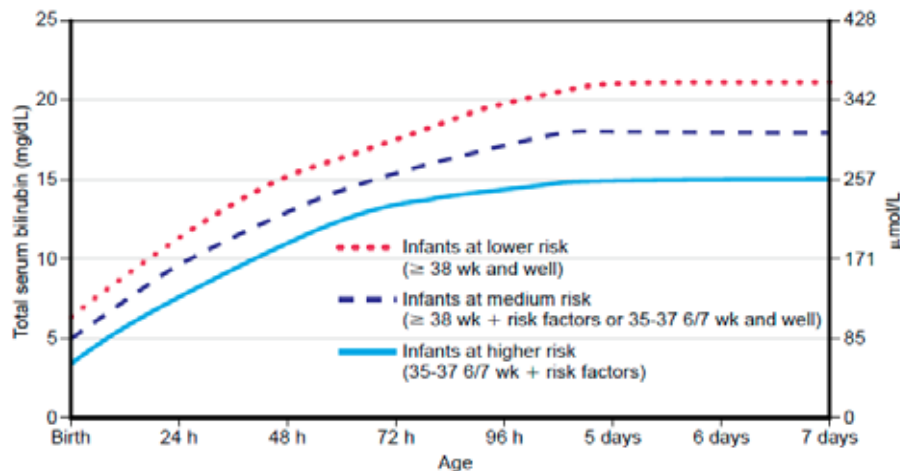
Idea

Exposure to blue-green spectrum (wavelengths 430-490 nm) → photo oxidises and isomerizes bilirubin → convert insoluble unconjugated bilirubin to non toxic, soluble forms → ↑ excretion via urine and bile

Indications

1. Treat moderately severe indirect hyperbilirubinemia in order to reduce need for exchange transfusion (In healthy full term at TSB 15-25 mg/dl and at lower levels in preterm and neonate with risk factors for kernicterus)
2. During waiting for exchange transfusion.

There is no consensus regarding exact bilirubin level at which to initiate phototherapy, so, Protocols using bilirubin nomogram , physical examination, and risk factors for kernicterus help decide the appropriate modality



Procedure

- Baby is completely naked except eyes and genitalia
- Change position every now and then
- Continuous exposure with short intervals for feeding
- Monitor temperature and hydration state frequently
- Monitor TSB every 4-24 hours according to infant's age ,condition and TSB level
- Discontinue when TSB fall 1.5-3 mg/dL below the level triggered the initiation of phototherapy



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- Fiber optic blankets (Bili blankets) are recently used for home or hospital phototherapy in prolonged cases
- Follow up TSB 6-12 hr after cessation of phototherapy



Side effects

1. Loose stool
2. Skin rash and erythema of skin
3. Hyperthermia
4. Dehydration due to insensible water loss
5. Damage to exposed eye or genitalia
6. If used in direct hyperbilirubinemia → Bronzed baby syndrome

2. Exchange transfusion

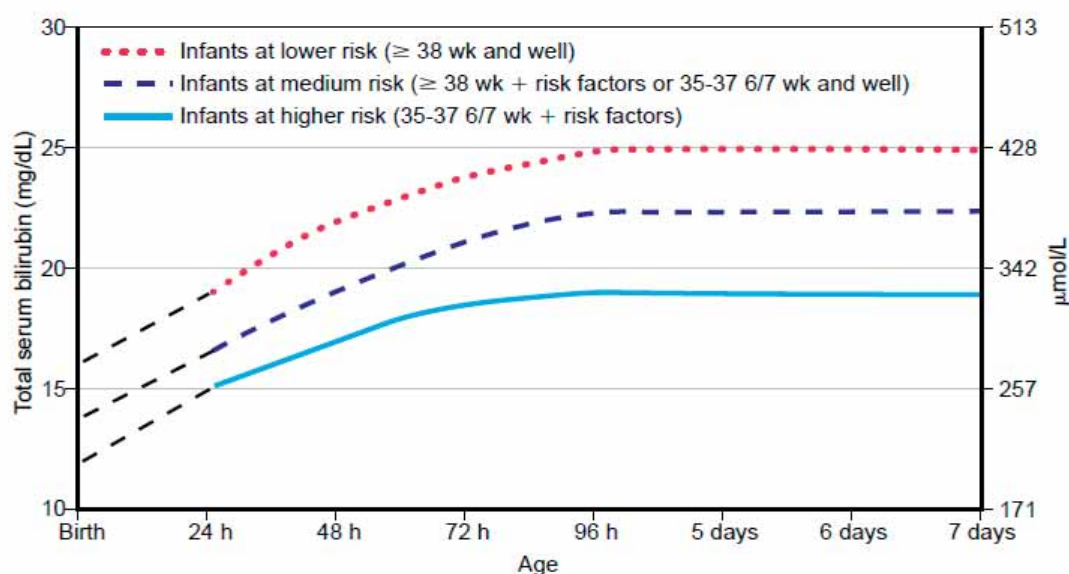
Indications

1- In Rh and ABO incompatibility

- Cord bilirubin > 5 mg/dl (normally < 3 mg/dl)
- Cord hemoglobin < 10 gm/dl
- Rapid rise of bilirubin (> 1 mg/dl/hour) despite phototherapy
- Early signs of kernicterus
- Previous baby with kernicterus or severe erythroblastosis fetalis

2- In other causes: with high bilirubin level & phototherapy ineffective

- Healthy full term TSB → ≥ 25 mg/dL
- Preterm and neonate with risk factors for kernicterus → at lower levels (reference tables & bilirubin nomograms also exist)



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Idea

- Remove excess unconjugated lipid soluble bilirubin.
- Remove antibodies from the circulation

Procedure

- Extensive phototherapy while preparing for the exchange
- Blood used is:
 - Fresh, warm O negative blood
 - Compatible with both maternal and neonatal blood
- Amount = double the neonate blood volume ($2 \times 85 \text{ ml/kg}$).
- Small amounts (10-20 ml) are removed and replaced by equal amounts of the new blood through umbilical vein catheter
- Potential complications include apnea and bradycardia in preterm infants, hypocalcemia, thrombocytopenia, metabolic acidosis, and vascular spasm

**3. Special Cases****a. Treat risk factors for kernicterus e.g.**

- Antibiotics for septicemia
- Correction of acidosis
- Avoid drugs which displace bilirubin from albumin

b. Breast milk jaundice

- Stop breast feeding for 24 - 48 hours → Bilirubin fall quickly

c. Isoimmune hemolytic disease

- Intravenous Immunoglobulin 0.5-1.0 g/kg/dose; repeat in 12 hr
- Reduce need for exchange transfusion in both ABO and Rh hemolytic disease

d. Crigler Najjar Syndrome type II

- Phenobarbitone 5 mg/kg/d oral.
- Role: Stimulates glucuronyl transferase enzyme (enzyme inducer).
- Side effect: sedation → poor feeding

e. Crigler Najjar Syndrome type I

- 1- Repeated exchange transfusion & phototherapy
- 2- Oral agar → block enterohepatic circulation of bilirubin.
- 3- Metalloporphyrin → block heme oxygenase.
- 4- Hepatic transplantation

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Kernicterus

(Bilirubin Encephalopathy)

Definition

Yellowish staining of the cerebellar & cerebral nuclei (especially basal ganglia) due to deposition of unconjugated bilirubin resulting in neuronal necrosis.

Etiology

A. Level of serum unconjugated bilirubin exceeding critical values

- > 10 mg/dl in the 1st day
- > 15 mg/dl in the 2nd day
- > 25 mg/dl afterwards

However kernicterus may occur at a lower levels in presence of risk factors:

a. Increased blood brain barrier permeability

- Prematurity & very low birth weight
- Acidosis
- Sepsis
- Asphyxia
- Anemia (Iso immune hemolysis ,G6PD ↓)

b. Defective albumin/ bilirubin binding

- Hypoalbuminemia < 3 gm /dl
- Hypothermia



B. Duration of exposure to the high bilirubin level:

The longer the duration the more risk of kernicterus.

Clinical picture

Usually appear 2-5 days after birth in term infants and by the 7th day in preterm

A. Acute bilirubin encephalopathy

Early signs

- Lethargy, poor feeding and Lost Moro reflex are common initial signs
- High pitched cry and hypotonia with diminished tendon reflexes
- Respiratory distress
- Seizures

Few days later

- Hypertonia of extensor muscles
- Opisthotonos with a bulging fontanel
- Fever



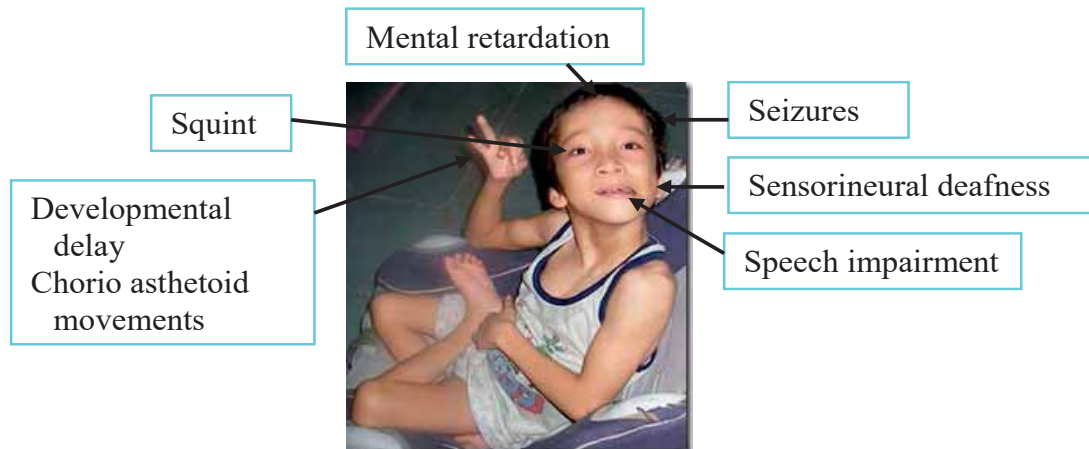
Many infants usually die during these phase

Survivors from previous phase go onto lucid interval for few months → there's apparent recovery or few symptoms.

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B. Chronic bilirubin encephalopathy

- Picture of Cerebral Palsy become apparent by the 1st -3rd year of life
- Type : chorio asthetoid or spastic cerebral palsy
- Clinical features:



- MRI of a patient with chronic bilirubin encephalopathy (kernicterus) is shown, revealing the classic symmetric high-intensity signal in the globus pallidus (arrows).



Management

a- Prevention

- * Adequate treatment of indirect hyperbilirubinemia (see before)
- * Prevention and treatment of risk factors: e.g. sepsis, acidosis, asphyxia, ...

b- Treatment

Acute

- Immediate Exchange Transfusion is mandatory once kernicterus is suspected
- Extensive phototherapy while waiting for exchange and after exchange
- Close monitoring of TSB and serum albumin to tailor further management plan
- Investigate for and treat risk factors e.g. sepsis ,anemia, cephalhematoma

Chronic

Not curable, need only supportive treatment for cerebral palsy.

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Conjugated Hyperbilirubinemia

Definition: Rise of total serum bilirubin with the conjugated fraction $> 15\%$ of total Or $> 2 \text{ mg/dl}$

Cholestasis: Means retention of conjugated bilirubin as well as other constituents of bile (e.g. bile salts)

Causes

1. Defective secretion of conjugated bilirubin by hepatocytes

- a. Genetic - Rotor and Dubin Johnson syndrome
- b. Acquired: (Neonatal hepatitis) due to:
 - * Infections : - Congenital infections e.g. TORCH
 - Neonatal sepsis.
 - Viral hepatitis : Echo, Herpes, EBV, Rarely HBV, HCV.
 - Idiopathic neonatal hepatitis
 - * Metabolic : - α_1 antitrypsin deficiency (13 %)
 - Galactosemia
 - Tyrosinemia

2. Defective excretion due to bile flow obstruction

- ⊕ Intrahepatic:
 - Congenital intrahepatic biliary atresia.
 - Intrahepatic biliary paucity (hypoplasia) e.g. Allagile syndrome
- ⊕ Extrahepatic:
 - Congenital extrahepatic biliary atresia.
 - Inspissated bile syndrome (Bile plug)

Clinical features

1. Color of sclera → Greenish or muddy yellow
2. Color of urine → Dark (bilirubinuria).
3. Color of stool → Pale (or clay).
4. Possible concurrent associations:
 - Hepatosplenomegaly.
 - Liver cells dysfunction.
 - Malabsorption and failure to thrive
 - Underlying systemic disease e.g. inborn error of metabolism, sepsis, TORCH.
 - No risk of kernicterus.

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5. Timing

* In 1 st day of life	- TORCH infection
* In the rest of 1 st week of life	- Neonatal sepsis - TORCH infection
* Persistent during 1 st month	- Neonatal hepatitis (metabolic or infections) - Congenital biliary atresia. - Inspissated bile syndrome

Investigations

- Liver function tests.
- Liver scan (HIDA scan).
- Liver biopsy.
- Metabolic screen for inborn errors of metabolism.
- TORCH screen.
- Sepsis screen

Treatment**i. Curable causes**

- Sepsis → antibiotics.
- Galactosaemia → lactose free milk.
- Extra hepatic biliary atresia → Kasai operation (hepato-porto- enterostomy)

ii. Supportive

- Formulas with medium chain triglycerides
- Fat soluble vitamins
- Water soluble vitamins
- Bile acid binders (Cholestyramine) oral → ↓serum cholesterol & bile acids.
- Minerals (e.g. calcium, phosphate).
- Liver transplantation for end stage liver failure.

Inspissated Bile Syndrome

- Persistent jaundice in newborns with elevations of both direct and indirect bilirubin after a period of increased indirect bilirubin
- It may be associated with massive hemolysis (Rh incompatibility), or hemorrhage (intraabdominal, intracranial, or retroperitoneal)
- Steroids & phenobarbitone may be tried in treatment

Haemolytic Disease of the Newborn (HDN) (Erythroblastosis Foetalis)

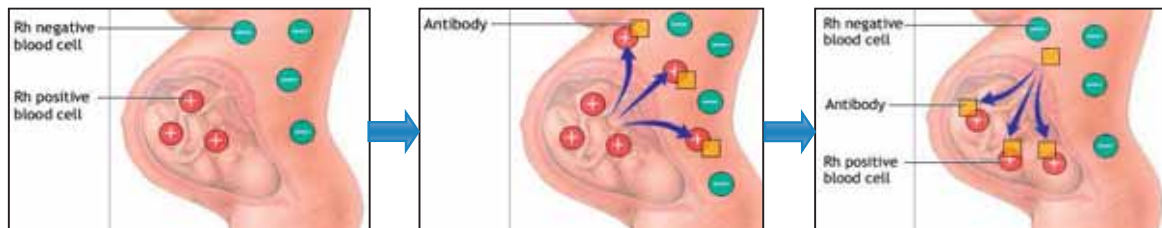
Etiology

Hemolysis of neonatal RBC's due to transplacental passage of maternal antibodies active against fetal RBCs. It includes:

1. Rh incompatibility; the mother is Rh negative and the baby is Rh positive
2. ABO incompatibility; the mother is usually group O and the fetus group A or B

Rh Incompatibility

Pathophysiology



- Escape of small amount of Rh +ve fetal blood (inherited from Rh +ve father) to the circulation of Rh -ve mother → maternal sensitization → formation of maternal anti-Rh antibodies (IgG) which crosses the placenta → Destruction of fetal RBCs
- The first baby usually escape hemolysis as sensitization usually occur near time of delivery, but the 1st baby may be affected if the mother was already sensitized e.g. with previous:
 - Amniocentesis
 - Blood transfusion
 - Chorionic villus sampling
 - Dead fetus (Miscarriage)
 - Ectopic pregnancy

Clinical features: According to severity; different presentations may occur:

1. Severe hemolysis (Hydrops fetalis)

- Due to severe intrauterine hemolysis → severe anemia
- Compensatory extramedullary hematopoiesis → huge hepatosplenomegaly.
- Failure of compensation → anemic heart failure with:
 - Severe pallor.
 - Severe respiratory distress.
 - Massive generalized edema (skin, ascites, pleural effusion, pericardial effusion, polyhydramnios and placental edema)
 - Stillbirth or death short after birth



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2. Moderate hemolytic; present by:-

- Anemia at birth worsening rapidly over the 1st day with hepatosplenomegaly
- Marked indirect hyperbilirubinaemia develops within few hours and progresses rapidly.
- Cases untreated usually die due to either kernicterus or anemic heart failure.

3. Mild hemolysis

- Mild hemolysis → mild anemia peaking at end of 3rd week.
- Unconjugated hyperbilirubinaemia at range of 16-20 mg/dl.
- May be splenomegaly.

Management**I. Postnatal management**

Diagnosis : Immediately ,after the birth of any infant to an Rh-negative woman, Do:

- Blood group ABO and Rh
- Hemoglobin
- Baseline serum indirect bilirubin
- Direct Coombs test
- Monitor hemoglobin and indirect bilirubin every 6-8 hours

Management**1. For hydrops fetalis:**

- Expert resuscitation
- Assisted /Mechanical ventilation
- Exchange transfusion with packed RBCs.
- Assist heart: Inotropes
- Correct hypoglycemia and hypocalcemia
- Correct acidosis

**2. For indirect hyperbilirubinemia**

A. Phototherapy in milder cases

B. Exchange transfusion

* Indications (see before)

* The blood used should be: Fresh and ABO-compatible with the mother and infant

3. Intravenous gamma globulin (inhibit hemolysis)

- Dose: 0.5gm/kg/dose; repeat in 12 hr
- Reduce the rate of hemolysis and the need for exchange transfusion in both ABO and Rh hemolytic disease

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II. Antenatal management (Prevention)

A. First pregnancy

* IM Anti-D (RhoGam) is given provided:

- The mother is Rh D negative
- The fetus is Rh D positive
- There is no maternal anti-D detectable in the mother's serum

* Regime:

- One dose at 28 - 32 weeks' gestation
- Another dose is given within 72 hours of delivery.

* Other situations e.g. ectopic pregnancy, threatened miscarriage

- One or more Anti-D doses

B. Subsequent pregnancies OR previous sensitization suspected

- Check anti-Rh.(anti D) titer in maternal blood by indirect Coomb's test
Starting at 12-16 weeks gestation



- If High OR rising titer → Check for fetal hemolytic disease by:

- A. Doppler flow velocity of the fetal middle cerebral artery (in moderate to severe anemia it demonstrates an increase in the peak velocity of systolic blood flow)



And

- B. Ultrasonography for fetal well being and signs of hydrops



- If the infant appears to have severe anemia or Fetal hydrops before 35 weeks gestation



Percutaneous Umbilical Blood Sampling (PUBS) is indicated to confirm hemolysis directly and if necessary, an intravascular fetal O negative Packed RBCs transfusion is given

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ABO Incompatibility

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies present	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens present	A antigen	B antigen	A and B antigens	None

Path physiology

- Occur when the mother blood group is O and the baby blood group is A or B.
- Maternal blood contain naturally present Anti-A and anti-B antibodies
- Maternal Anti-A and anti-B antibodies are usually of IgM type that is unable to cross the placental barrier, but in 10 % of cases these antibodies are of IgG type that can escape placental barrier and affect the baby

Clinical criteria

- As antibodies are naturally present; the 1st baby may be affected
- Milder course
- Direct Coomb's test is weak positive
- Mild spherocytosis
- If ABO and Rh incompatibility coexist: Maternal preexisting anti-A or anti-B antibodies rapidly remove fetal Rh-positive cells from her circulation → mother is partially protected against sensitization

Treatment

- o Phototherapy
- o IVIG
- o Exchange transfusions with type O blood of the same Rh type as the infant
- o Some infants with ABO hemolytic disease may require transfusion of packed RBCs at several weeks of age because of slowly progressive anemia.

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Self-assessment Quiz

Case 9

A 5-day-old, large-for-gestational-age, 4500-g boy has a bilirubin level of 15 mg/dL. There is no anemia or polycythemia. Examination apart from a moderate cephalohematoma is normal

- a. What is the diagnosis?
- b. What is the required treatment?

Case 10

Female newborn, second kid, aged 4 days, weight 3.900 kg, presented with neonatal jaundice noticed on the 3rd day of life. Examination reveal entirely normal adequately breast fed newborn, slight pallor, but no organomegaly

Investigations :

Indirect bilirubin level 19 mg/dl
 Baby blood group A , Rh negative
 Mother blood group O , Rh positive.
 Baby hemoglobin 11 gm/dl

- a. Suggest a diagnosis
- b. What are further investigations required?

Case 11

A 6 days old, 36 week gestation male presents to his physician with worsening jaundice. He was discharged home on day 2 of life after successfully breastfeeding for a 24 hour period. At the time of discharge, his physical exam was unremarkable

Findings :

He is markedly jaundiced but otherwise normal
 Fair urine output and yellow stools
 Maternal and infant blood type is A +
 The total bilirubin is 27 mg% with a direct fraction of 1 mg%
 The hematocrit is 47% with a reticulocyte count of 1%

- a. What is the diagnosis?
- b. Treatment?

Case 12

This is a term female born by forceps assisted vaginal delivery to a primiparous woman , now she is 96 hours old ; she is not interested in feeding as before , sleepy all the time and has frequent eye staring and mouth twitches described as subtle seizures. Investigations

Indirect bilirubin level 26.5 mg/dl
 Baby blood group A , Rh negative
 Mother blood group O , Rh positive.
 Baby hemoglobin 11 gm/dl
 Reticulocyte count 5%

- a. What is the diagnosis?
- b. What are the required investigations?
- c. Management?



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Hemorrhagic disease of the newborn

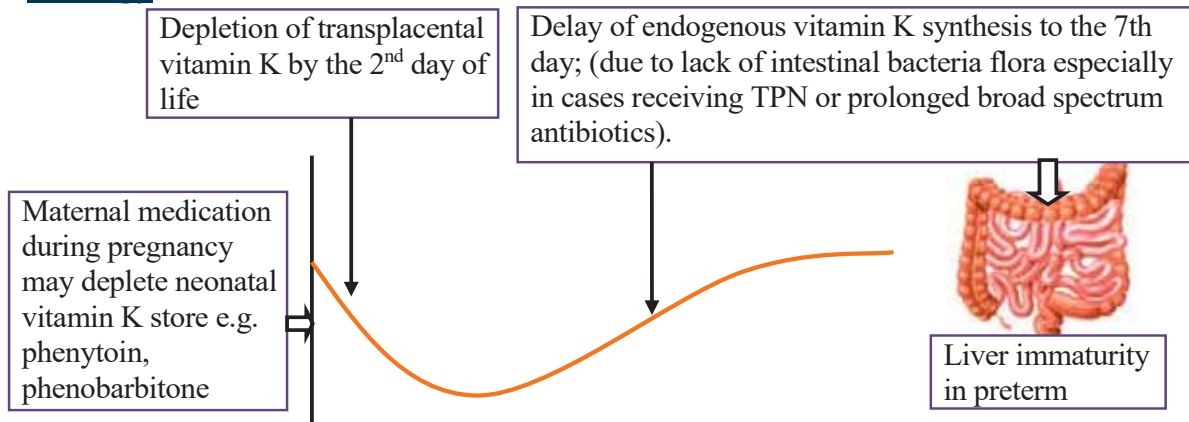
Definition

Hemorrhagic disorder in early neonatal period due to deficiency of vitamin K dependant clotting factors (II, VII, IX, X).

Incidence

- Affect about 2% of neonates not given vitamin K at birth
- Preterm and Breast milk feeders are more at risk than formula feeder full term.

Etiology



Clinical picture

1. Bleeding tendency:

* Timing?	- Usually between the 2 nd - 7 th day of life (may be early or late).
* Sites ?	- Commonly gastrointestinal, umbilical, or circumcision site - Rarely internal hemorrhage
* Look ?	- The baby looks well except if there is severe hemorrhage or intra cranial hemorrhage.

2. May be hemorrhagic anemia (pallor, tachycardia up to shock).

Investigations

- Prolonged prothrombin time (P.T.) and partial thromboplastin time (P.T.T)
- Deficiency of vitamin K dependant factors
- Normal bleeding time and platelet count

Prevention

- Vitamin K₁ 1 mg , intra muscular at birth
- Oral vitamin K is less effective

Treatment

- Vitamin K₁ 1-5 mg intravenous daily for 3 days
- Fresh plasma transfusion for preterm , liver diseases and active bleeding
- Fresh blood transfusion in severe bleeding.

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Neonatal Anemia

Definition

A hemoglobin value less than the normal range of hemoglobin for birthweight and postnatal age

A. Physiologic anemia of infancy

At term

- Hemoglobin is 14-20 gm/dl (1-2 gm/dl lower in VLBW) and Htc. value 55% Due to relative intrauterine hypoxia → ↑ erythropoietin → ++ Bone marrow → higher hemoglobin at term
- As oxygen saturation improves after birth → ↓ erythropoietin production → Hemoglobin continue to decline to reach a nadir of 11 gm/dl at about 8-12 weeks of age (7-10 gm/dl in preterm) → re stimulation of erythropoietin release .

Clinically

- * Usually there is no clinically detectable pallor
- * Anemia is self resolving, so usually requires no treatment

Prevention

Delayed clamping of the umbilical cord (≈1-2 min) with the infant held below the level of the placenta may enhance placental-infant transfusion and reduce postnatal transfusion needs; it provide extra 20-40 mL of blood and 30-35 mg of iron

B- Pathologic anemia

Blood loss	Hemolysis	↓ RBCs production
With normal reticulocyte count	With reticulocytosis	With reticulocytopenia
<ul style="list-style-type: none"> - Twin to twin transfusion - Feto-maternal transfusion - Placental malformations 	<ol style="list-style-type: none"> 1. <u>Immune hemolysis</u> <ul style="list-style-type: none"> - Rh incompatibility - ABO incompatibility 2. <u>Hereditary hemolysis</u> <ul style="list-style-type: none"> - Spherocytosis. - G6PD deficiency - α-thalassemia 	<ul style="list-style-type: none"> - Congenital infections - Congenital leukemia - Pure red cell anemia
<u>After delivery</u> <ul style="list-style-type: none"> - Frequent sampling. - Neonatal hemorrhage whether internal or external 		

Treatment

- Packed RBC's transfusion (15-20 ml/kg over 2- 4 hours)
- Blood transfusion threshold depends on the severity of symptoms, hemoglobin level, and presence of co-morbid diseases (e.g. cyanotic congenital heart disease, respiratory distress syndrome) that interfere with oxygen delivery;
- At Hb% ≤ 11 for neonate on mechanical ventilation
 - At Hb% ≤ 10 for neonate on minimal respiratory support

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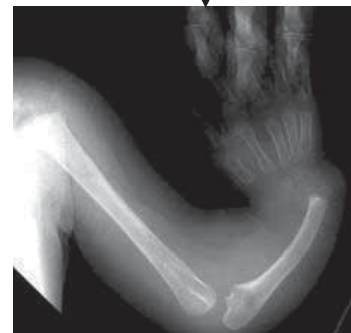
- At Hb% ≤ 8 for neonate on supplemental O₂ with poor weight gain or apnea
- At Hb% ≤ 7 for Asymptomatic neonate
- Treatment of the cause e.g. Vitamin K for hemorrhagic disease of newborn

Neonatal bleeding

Causes

a. Bleeding in Otherwise Well Newborns

- Pseudohemorrhage in the Newborn
 - Fresh blood coming from the stomach of a newborn may be of fetal or maternal origin (swallowed maternal blood)
 - Apt test of the blood, based on maintenance of pink color of fetal but not adult hemoglobin diluted in 1% sodium hydroxide, can help determine the origin of blood cells
- Platelet Disorders
 - Neonatal Alloimmune Thrombocytopenia (Maternal antibodies directed against fetal antigens)
 - Maternal Immune Thrombocytopenia Purpura
 - Congenital thrombocytopathy
 - Congenital Thrombocytopenia e.g.
 - Thrombocytopenia with absent radius syndrome (TAR)
 - Fanconi anemia (FA)
 - Wiskott Aldrich syndrome
- Hemophelias
- Vitamin K deficiency
- Local bleeding e.g. with NGT, thermometer



b. Bleeding in sick neonate

- Disseminated intravascular coagulation
- Liver disease
- Necrotizing enterocolitis
- Serious bleeding due to any cause

Workup

- Diagnosis and choice of an investigation depends on the newborn general condition, clinical pattern of bleeding, maternal and family history
- Basic workup includes:
 - Coagulation profile (PT, PTT, D-Dimer)
 - CBC with blood film for platelet count and morphology
 - Specific e.g. specific clotting factor assay

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Perinatal asphyxia

Definition

Acute or chronic impairment of gas exchange with hypoxia, hypercapnia and acidosis with consequent organ damage. The term Hypoxic Ischemic Injury (HII) has replaced the term of perinatal asphyxia

Causes

Impairment in oxygenation and perfusion due to

- Impaired placental supply due to placental insufficiency, placental abruption and uterine contractions
- Impaired umbilical supply due to cord compression/prolapsed or knots
- Impaired materno-placental supply due to maternal hypoxia or hypotension
- Impaired neonatal supply due to difficult delivery or inadequate resuscitation
- Post-natal causes (uncommon):
 - Severe congenital cyanotic heart diseases.
 - Severe anemia due to severe hemorrhage or severe hemolysis

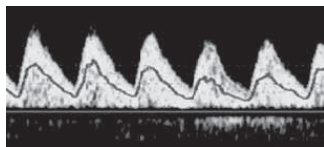
Clinical picture

Depends on duration & severity of asphyxia

I. In the fetus

Indicators of fetal hypoxia and distress include:

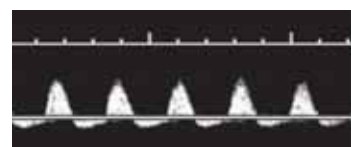
- 1- Intrauterine growth restriction may indicate chronic hypoxia
- 2- Umbilical artery Doppler shows absent or even reversed end-diastolic flow suggesting severe fetal circulatory compromise



Normal end diastolic flow

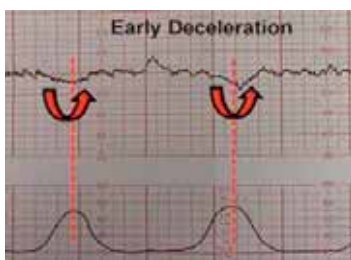


Absent end diastolic flow

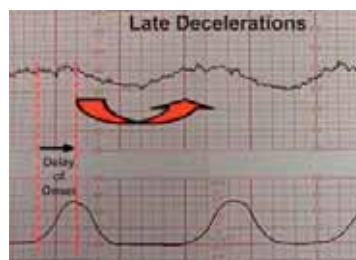


Reversed end diastolic flow

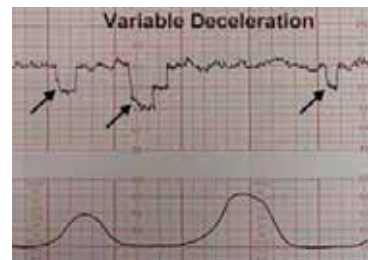
- 3- Continuous heart rate recording may reveal a variable or late deceleration pattern (decrease in fetal heart rate beginning at or after the peak of the contraction and returning to baseline only after the contraction has ended)



Early Deceleration



Late Decelerations



Variable Deceleration

- 4- Acidotic scalp or cord pH

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II. After delivery

- 1- Meconium staining of the newborn, amniotic fluid and vernix caseosa
- 2- Decreased consciousness and failure of spontaneous breathing.
- 3- Low Apgar score with cyanosis and flaccidity

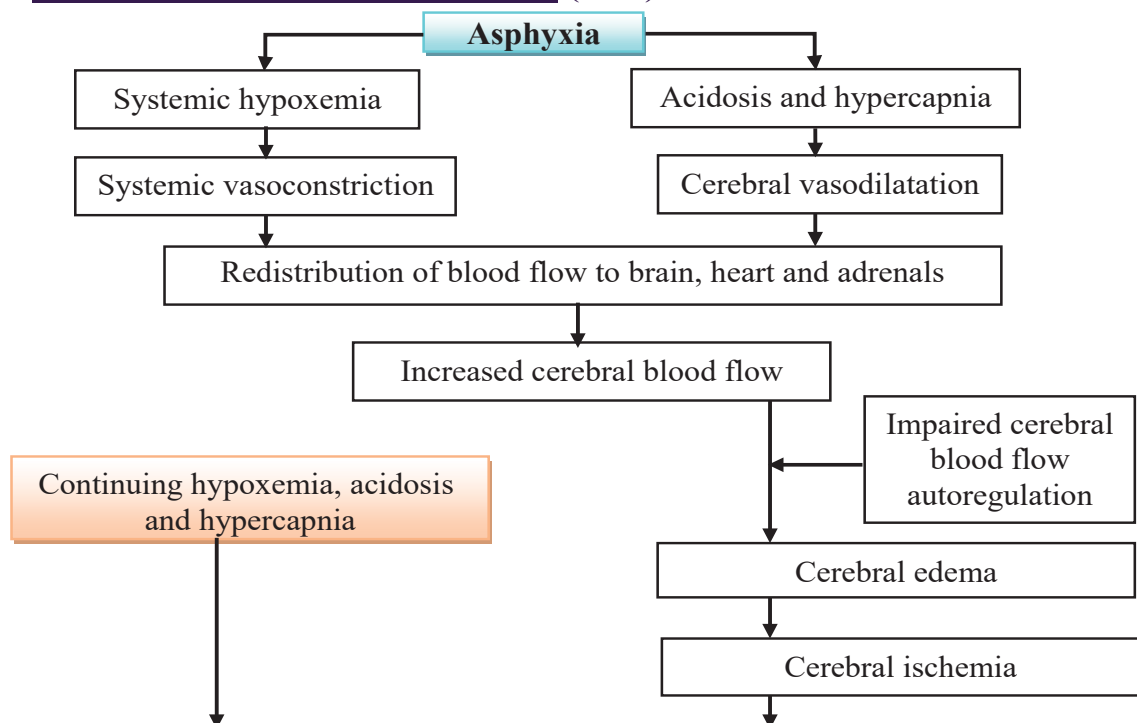


III. Later Neurologic and Multi Organ Dysfunction

American academy of pediatrics define severe asphyxia as combination of

- Low Apgar score < 4 for at least 5 minutes
- Umbilical artery pH < 7.00 (if obtained)
- Neurological insults e.g. seizures
- Multiorgan insults : Cardiac ,pulmonary ,renal or intestinal

1. Hypoxic-ischemic encephalopathy (HIE)



Brain cell injury

- Early phase (minutes – 6 hours)
 - Anaerobic glycolysis → intracellular energy failure → necrotic cell death
 - Increased GABA
 - Release of excitatory amino acids particularly glutamate
- Late phase (6-72 hours)
 - Release of neurotoxic mediators e.g. free radicals and nitric oxide → apoptotic cell death

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Sarnat and Sarnat clinical grading of HIE

Sign	Mild (I)	Moderate (II)	Severe(III)
○ Autonomic	Sympathetic	Parasympathetic	Depressed
○ Consciousness	- Hyper alert	- Lethargy	- Comatose
○ Muscle tone	- Normal	- Hypotonic	- Flaccid
○ Suckling reflex	- Weak	- Weak	- Absent
○ Moro reflex	- Exaggerated	- Weak	- Absent
○ Pupils	- Dilated	- Miotic	- Often unequal
○ HR	- Tachycardia	- Bradycardia	- Variable
○ Seizures	- None	- Common	- Decerbrate
○ EEG	- Normal	- Abnormal	- Abnormal (isopotential)
○ Duration	1-3 days	2-14 days	- Hours to weeks
○ Out come	Good	Variable	- Death or severe deficits

2. Cardiac → Heart failure, cardiogenic shock

3. Respiratory → Meconium aspiration ,apnea, pulmonary hypertension

4. Renal → Oliguria, hematuria, Acute tubular necrosis

5. GIT → Necrotizing enterocolitis

6. Hematologic → DIC

6. Metabolic → Hypoglycemia , hypocalcemia ,hypomagnesemia, hyponatremia and syndrome of inappropriate secretion of ADH

Diagnosis :

There are no specific tests to neither confirm nor exclude a diagnosis of HII

Diagnosis is made based on the history, physical and neurological examinations

1. Neuro imaging

- Brain MRI
 - Modality of choice for the diagnosis and follow-up of HIE
 - Early detection of brain edema and brain injury (basal ganglia)
 - Conventional MRI show changes by the 3rd day
 - Diffusion Weighted MRI shows changes in the 1st 24 hours (*preferred*)
- Cranial ultrasonography
 - Less sensitive than MRI (initial scan is negative in up to 50% of cases)
 - Perform on day 1 then as guided by clinical condition

2. EEG

- Both standard EEG and amplitude integrated (aEEG) are used
- Detects seizures and evaluate the degree of encephalopathy

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Management

A. In delivery room

- 1- Avoid and treat risk factors
- 2- If fetal distress: provide high flow oxygen & prepare for immediate delivery
- 3- Neonatal resuscitation according to neonatal life support guidelines
- 4- Assess severity of encephalopathy

B. In NICU

1. Therapeutic Hypothermia

Idea: Moderate hypothermia in perinatal asphyxia is neuroprotective

Neuroprotection via:

- Reduced metabolic rate and energy depletion
- Decreased excitatory transmitter release
- Reduced apoptosis
- Reduced vascular permeability, and edema.

Eligibility

- ≥ 36 weeks gestation
- < 6 hours old
- Evidence of moderate to severe encephalopathy (Sarnat)
- Evidence of perinatal asphyxia; one of the following
 - Apgar ≤ 5 at 10 minutes
 - Continuing resuscitation at 10 minutes
 - pH < 7.00 in the first hour
 - Base Excess ≤ -16 in the first hour

Method

- Resuscitation as usual
- Start selective head cooling (using CoolCap) or total body cooling (systemic).
- Rectal temperature is then maintained at $34-35^{\circ}\text{C}$ for 72 hours.
- Rewarming is carried out gradually, over 6-8 hours.



2. Supportive care

Ventilation

- Consider ventilatory support early
- Ensure adequate oxygenation; avoid hyperoxia
- PaCO₂ between 35 - 45 mmHg is neuroprotective
- Treat pulmonary hypertension if exist

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Cardiovascular

- Consider invasive blood pressure monitoring
- Maintain mean arterial blood pressure above 35-40 mm Hg in term to ensure adequate cerebral perfusion
- Consider inotropic support early ; start with dobutamine infusion and add dopamine if required
- Fluid boluses if hypovolemic
- Monitor Hb% ; acute fall may indicate new intracranial hemorrhage
- ECG and Echo if there is concern over poor cardiac function

Fluids

- Fluid balance based on weight, urine output, serum sodium & renal function
- Initially fluid restrict to 60-80 % maintenance and liberalize as urine output improve

Neurology

- Treat seizures even asymptomatic (i.e., seen only on EEG)
- Phenobarbitone is the drug of choice

Metabolic

- Maintain normoglycemia
- Treat hypocalcemia

Coagulation

- Send coagulation screen; PT, PTT, D-dimer and platelets
- Correct any coagulopathy with Vit K ,FFP, cryoprecipitate or platelets

Feeding

- Withhold enteral feeds for the first 3 days
- Introduce feeds cautiously when clinical condition has improved
- Increase feed volumes slowly
- Monitor for necrotizing enterocolitis

Withdrawal of care

- May be appropriate for severe HIE who have iso electric/burst suppression in EEG and abnormal cerebral blood flow on Doppler
- Active treatment should be continued at least for the first 24 hours

Prognosis

About 20-30% of infants with HIE die in the neonatal period
≈ 33-50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, mental retardation).

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Neonatal Seizures

Definition

Paroxysmal alterations of neurologic functions including motor, behavioral and / or autonomic changes

Causes

A. Central nervous system

- Incidence: the commonest causes, includes:
 - Hypoxic-ischemic encephalopathy (the commonest cause in term babies).
 - Intra cranial hemorrhage (intraventricular, parenchymal, subarachnoid or subdural)
 - Sepsis (meningitis, encephalitis, tetanus, TORCH)
 - Congenital brain malformations e.g. cerebral dysgenesis (5%).
 - Bilirubin encephalopathy (Kernicterus)
 - Neuro-cutaneous syndromes e.g. tuberous sclerosis, incontinentia pigmenti

B. Metabolic

1. Hypoglycemia
 - Blood glucose less than 2.6 mmol/l (\approx 45 mg/dl)
 - Causes: infant of diabetic mother (IDM), preterm, asphyxia , hypopituitarism, Erythroblastosis fetalis, galactosemia
2. Hypocalcaemia
 - Serum calcium less than 7mg/dl which either:
 - Early onset (in 1st 3 days) → due to IDM, preterm, & asphyxia.
 - Late onset (after end of 1st week) → due to decrease calcium intake, hyper phosphatemia, and hypoparathyroidism.
3. Hypomagnesemia (< 1.5 mg/dl) → often associated with hypocalcaemia
4. Hyponatraemia (< 135 meq/L) or hypernatraemia (> 150 meq/L)
5. Inborn errors of metabolism: e.g.
 - Galactosemia
 - Hyperammonemia
 - Organic acidemia

C. Other causes

- Pyridoxine or pyridoxal (vitamin B6) dependency (essential for GABA)
- Drug withdrawal e.g. maternal narcotics or addiction
- Theophylline toxicity
- Benign neonatal seizures (normal neonate ;diagnosed by exclusion)

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Clinical picture

Subtle seizures

The commonest type (50 %) occurs more commonly in premature than full term:

- Eye movements: eye rolling, eye deviation, staring, blinking or nystagmus
- Repetitive oral movements: suckling, chewing or lip smacking.
- Limb movements: pedaling, bicycling or boxing
- Autonomic: apnea, fluctuations in heart rate, hypertension episodes & desaturations

Clonic seizures

- Limb jerking
- Multifocal (rarely generalized due to decreased connectivity associated with incomplete myelination in neonates)

Myoclonic seizures

- Brief sudden, shock like jerking movements of limbs

Tonic seizures

- Focal: persistent posturing of a limb or trunk or neck often with persistent horizontal eye deviation.
- Generalized: bilateral tonic limb extension or tonic flexion of upper extremities often associated with tonic extension of lower extremities

Spasms

- Very brief sudden generalized jerks lasting 1-2 sec
- Distinguished from generalized tonic spells by their shorter duration

Approach to diagnosis

a. History

- Onset of convulsions
 - * In the 1st 4 days of life: e.g. HIE, drug withdrawal, or metabolic causes.
 - * After the 4th day: e.g. intra cranial hemorrhage and metabolic causes.
 - * After the 1st week: e.g. sepsis (meningitis).
- Course and duration of convulsions
- Perinatal insults:
 - Maternal diseases, medications or addiction
 - Birth trauma
 - Evidence of asphyxia
- Family history for benign neonatal seizures or inborn errors of metabolism

b. General examination

- Search for cranial birth trauma or congenital head anomalies
- Signs suggestive of sepsis or congenital infections

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- Severe hyperbilirubinemia plus risk factors → kernicterus
- Abnormal Smell → metabolic causes
- Skin examination e.g. for hypomelanotic patches of tuberous sclerosis
- Retinal examination for chorioretinitis in TORCH

c. Neurologic examination

- Pattern of convulsions
- Signs of raised intra cranial tension e.g. tense fontanel

Investigations

- Check initially for blood glucose, calcium, magnesium, sodium, blood gases
- Sepsis Screen: complete blood picture, CRP, blood culture.
- CSF analysis: - For glucose, protein, Gram stain, culture and viral PCR
- Delay lumbar puncture if the baby is unstable
- TORCH Screen for suspected cases
- Neuro imaging : - Cranial ultrasound excludes intra cranial hemorrhage
- CT/MRI for brain malformations, and infarcts
- Electroencephalogram (EEG)
- Metabolic Screen if acidotic or family history: e.g. ammonia, amino acids, lactate, urine amino acids and organic acids
- Karyotyping for dysmorphic babies

Differential diagnosis

Seizures should be differentiated from **Jitteriness** which is characterized by:

- Tremor like movements of limbs
- Precipitated by sensory stimuli.
- Stopped by holding the limb.
- No associated autonomic changes, ocular phenomena or EEG changes
- Seen in normal infant, drug withdrawal, hypocalcemia & hypoglycemia

Treatment

- Maintain ventilation which may be compromised during seizures and following anti convulsants
- Rapidly identify and treat reversible causes of seizures

- Hypoglycemia	→ Glucose 10% I.V 2- 4 ml/kg
	→ May require continuous glucose infusion
- Hypocalcemia	→ Calcium gluconate 10% slow I.V 2 ml/kg
- Hypomagnesemia	→ Magnesium sulphate 50% I.M 0.2 ml/kg
- Start parenteral antibiotics (± acyclovir) if there is any concern of sepsis

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○ Anti convulsants

Start an anticonvulsant if

- Seizure lasting > 5minutes
- Brief but frequent seizures > 3 /hour
- Prolonged desaturations
- Hemodynamic instability

First line: Phenobarbitone

- Loading dose 20 mg/kg IV
- If seizures continue at 30 minutes → give another 10 mg/kg IV and take blood for phenobarbitone level (Therapeutic phenobarbital levels are 20-40 µg/mL)
- If seizures remain uncontrolled → give further 10mg/kg IV (total 40 mg/kg)



If total loading dose of 40 mg/kg of phenobarbitone was ineffective

Second line : Phenytoin

- Loading dose 20 mg/kg slow IV over 30 minutes
- Monitor heart rate and blood pressure closely
- Better avoided in babies with poor cardiac function



Third lines

Lorazepam

- 0.05 mg /kg IV repeated every 6-8 hours
- Usually, it does not cause hypotension or respiratory depression

Midazolam

- 0.05-0.1 mg/kg IV, with a continuous infusion of 0.5-1 micg/kg/min IV
- Carry risk of hypotension and respiratory depression



If poor response to previous treatment

Therapeutic trials

- Pyridoxine or pyridoxal phosphate 100-200 mg IV with real time EEG
- The seizures abruptly cease, and the EEG normalizes in the next few hours
- If there is negative response to IV pyridoxine ,try:
 - 1 week trial of pyridoxine 100 mg oral daily
 - 6 weeks of pyridoxal phosphate 30 mg/kg oral daily
 - Creatine 300 mg/kg daily + Folinic acid 2.5 mg bid + Biotin (10 mg od)

Maintenance treatment

- If seizures persist, use phenobarbitone 3-6 mg /kg in 2 divided doses started 24 hours after the loading dose
- Most will have stopped anticonvulsants except those with abnormal neurology

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Self Assessment Quiz

Case 13

A 4 days male infant presented in the outpatient department with bleeding from circumcision site. The child was the product of a full-term, normal pregnancy in a 25 year old mother with an uncomplicated antenatal period. Family history was negative for any form of hereditary or acquired bleeding disorder. He was delivered by spontaneous vaginal delivery at home without any intervention and was on exclusive breast feeds. Prothrombin time (PT) and partial thromboplastin time (PTT) done at that time were markedly elevated with hemoglobin 11.5 gm/dl

- a. What is the most likely diagnosis?
- b. What are the 3 most important lines of treatment?

Case 14

A full-term infant is born after a normal pregnancy; delivery, however, is complicated by marginal placental separation. At 12 h of age, the child, although appearing to be in good health, passes a bloody meconium stool. Intramuscular vitamin K was administered in the delivery room. Clinically the baby was well and all clotting indices and hemoglobin were normal

- a. What is the expected diagnosis?
- b. How to confirm?

Case 15

A female baby was born at 38 weeks of gestation by spontaneous delivery. Birth weight was 3470 g and Apgar score 1/3/3 (at 1 minute, 5 minutes and 10 minutes). After delivery, the baby needed immediate cardiopulmonary resuscitation with intubation, external cardiac massage, ventilatory assistance and an immediate blood transfusion for severe anemia (Hb 2.5 g/dL). Severe metabolic acidosis was present (pH 6.81), with arterial hypotension (41/19 mmHg)

- a. What is the clinical scenario?
- b. How can you predict neurologic outcome?

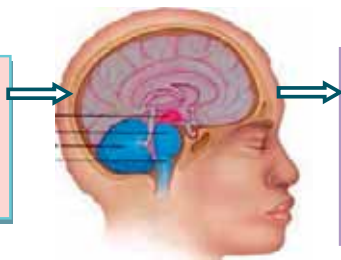
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Causes of Neonatal Respiratory Distress

I. Central

CNS failure: Due to

- Over sedation
- Perinatal asphyxia
- Intra cranial hemorrhage

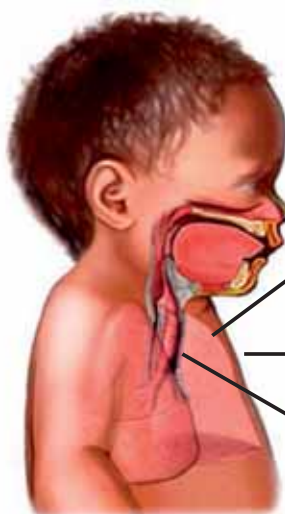


Manifested by:

- Slow, irregular, gasping respiration.
- Apneic attacks.
- Disturbed consciousness.
- Poor reflexes

II. Peripheral

A. Pulmonary



Lungs

- Transient tachypnea of newborn (TTN)
- Respiratory distress syndrome (RDS)
- Meconium aspiration syndrome (MAS)
- Congenital pneumonia
- Congenital lobar emphysema
- Lung collapse, Cysts, Hypoplasia

Pleura

- Air leak e.g. Pneumothorax
- Congenital diaphragmatic hernia (CDH)
- Pleural effusion.

Airways

- Vascular ring
- Bilateral choanal atresia

B. Extra Pulmonary

1. Cardiac



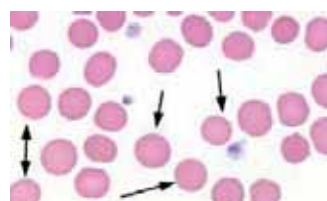
- Heart failure
- Duct dependent
- Congenital heart diseases
- Critical obstructive lesions

2. Metabolic



- Metabolic acidosis
- Hypoglycemia
- Hypothermia

3. Hematologic



- Anemia
- Polycythemia

Clinical signs of peripheral respiratory distress

Grade I	(Mild)	→	Tachypnea (> 60 / min) & working alae nasi
Grade II	(Moderate)	→	As mild <u>plus</u> intercostal & subcostal retractions
Grade III	(Severe)	→	As moderate <u>plus</u> grunting
Grade IV	(Advanced)	→	As severe <u>plus</u> central cyanosis, disturbed consciousness

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Initial management of babies presenting with respiratory distress

1. Resuscitation and ensure temperature stability
2. Pulse oximetry and supplemental oxygen
3. Chest radiograph : immediate if significant respiratory distress or delayed until 4 hours if mild respiratory distress
4. Review history : gestation, rupture of membranes, type of delivery, meconium stained amniotic fluid, maternal diabetes
5. If RDS suggested consider intubation and early surfactant and/ or CPAP
6. Assess for clinical improvement regarding:
 - Well/ unwell, pink/pale/blue
 - Perfusion
 - Signs of respiratory distress
 - Oxygen saturation



- Clinical improvement → observe over 10 - 20 minutes → if quiet tachypnea → consider TTN → routine neonatal care
- Consider echocardiography if lung fields in chest radiograph is clear
- Proceed to further support if any of the following exists:
 1. No clinical improvement
 2. Condition deteriorates
 3. Abnormal chest radiograph
 4. Infant requires > 40% oxygen to maintain saturation



- Establish IV access
 - Umbilical venous catheter and start IVF 60 ml /kg/day initially 10% dextrose
 - Consider umbilical arterial catheter for blood pressure monitoring and ABG analysis if the infant's inspired fraction of oxygen exceeds 40%
- Blood tests
 - Blood glucose
 - CBC with differential
 - CRP
 - Blood culture; Not helpful initially as results may take 48 hours
 - Blood gases
- Start IV antibiotic ; Benzylpenicillin (or Amoxicillin) and Gentamicin



Respiratory support (see RDS)

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Respiratory Distress Syndrome (RDS)

(Hyaline membrane disease)

Definition

A syndrome of respiratory distress occurs almost exclusively in premature due to surfactant deficiency

RDS is the commonest cause of neonatal death.

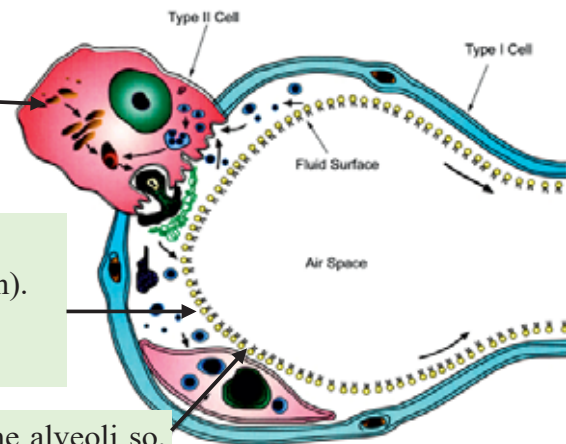
Surfactant

A lipoprotein produced by alveolar cells type II starting after 20th week of gestation and mature after 35th weeks (near term).

Composed mainly of:

- Dipalmitoyl phosphatidylcholine (Lecithin).
- Phosphatidyl glycerol.
- Surfactant proteins A, B, C & D

Functions: reduce surface tension within the alveoli so, prevent their collapse at the end of expiration and reduce the lung stiffness and work of breathing



Causes of RDS

1. Prematurity

- The leading cause of RDS
- Incidence & severity of RDS are related inversely to the gestational age of the newborn infant e.g. about 60% of prematures < 28 weeks develop RDS

2. Infant of diabetic mother

- Fetal cortisone is essential for surfactant production
- Maternal hyperglycemia → fetal hyperinsulinemia → ↓↓ fetal cortisone

3. Cesarean section (CS) and precipitate labor:

- Due to lack of stressful delivery → reduced fetal cortisone.

4. Intrapartum asphyxia

- Due to hypoxemia of alveolar cells type II.

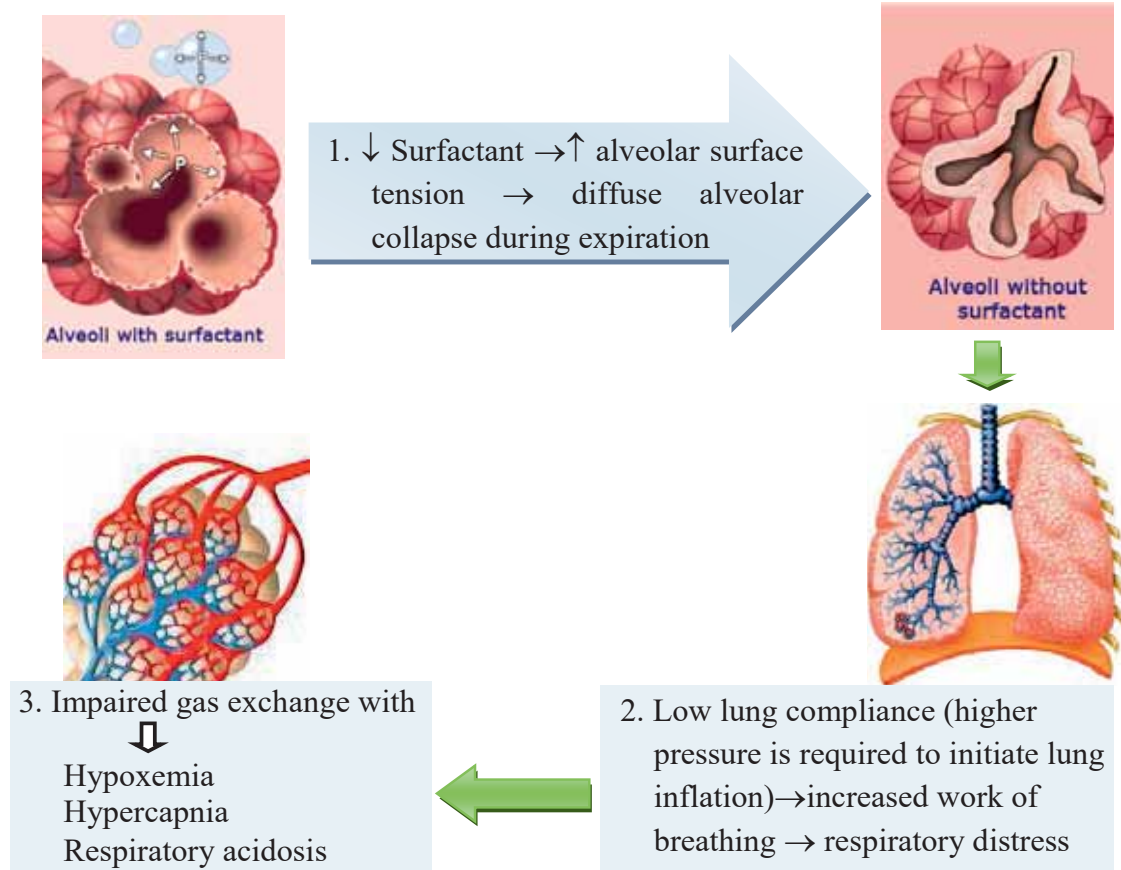
5. Others : Second twin, male Sex, RDS in Siblings

In contrast, the incidence of respiratory distress syndrome decreases with the following:

- Use of antenatal steroids
- Pregnancy-induced or chronic maternal hypertension
- Prolonged rupture of membranes
- Maternal narcotic addiction

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Pathophysiology



4. Hypoxemia → alveolar cells type II dysfunction → more surfactant deficiency
→ Progressive atelectasis

Clinical picture

- Progressive signs of respiratory distress are noted soon after birth and include the following:
 - Tachypnea
 - Nasal flaring
 - Expiratory grunting (from partial closure of glottis)
 - Subcostal and intercostal retractions
 - Cyanosis
 - Extremely immature in neonates may develop apnea and/or irregular respirations
 - Patients may also have edema, ileus, and oliguria

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○ Course

- Endogenous surfactant production usually become sufficient by 48-72 hours→ Clinical improvement is often heralded by spontaneous diuresis and improved blood gas values at lower inspired oxygen levels and/or lower ventilator support
- Severe cases may end in death or complications

Diagnosis

1. Clinical

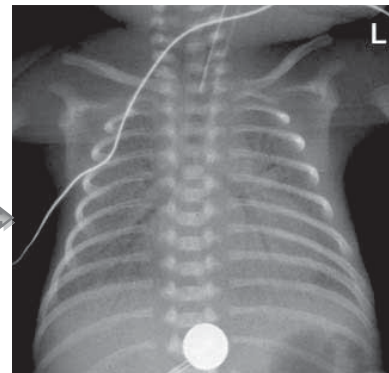
RDS is suspected clinically in cases with early respiratory distress in presence of risk factors particularly prematurity



2. Chest radiographs

A. Mild to moderate RDS

- Bilateral, diffuse, reticulo- granular infiltrates (ground-glass appearances)
- Air bronchograms represent aerated airways superimposed on a background of collapsed alveoli
- Poor lung expansion (small lungs volumes)



B. Severe RDS

Opacification of both lungs (White airless lungs)



3. Blood gases analysis

- In Milder RDS: Hypoxemia
- In Severe RDS: Hypoxemia + Hypercapnia + Respiratory acidosis



- #### 4. Sepsis workup: blood cultures, a complete blood count with differential, and C-reactive protein

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Fetal lung maturity tests

Prediction of fetal lung maturity is derived by:

1. Estimating Lecithin/sphingomyelin ratio in the amniotic fluid :
 - * If > 2 → Mature lung → No risk of RDS
 - * If 1.5-2 → Transitional lung → Risk of RDS
 - * If < 1.5 → Immature lung → Severe RDS
2. The presence of phosphatidylglycerol in the amniotic fluid → No risk of RDS

Differential diagnosis

Other causes of early neonatal respiratory distress e.g.

Early-onset sepsis (GBS pneumonia)

Cyanotic heart disease

Prevention of RDS

- Antenatal steroids to enhance pulmonary maturity & surfactant production
 - Recommended for:
 - Threatened preterm labour between 24-34 weeks gestation
 - Recently approved for late preterm deliveries (34 - 36⁺⁶)
 - Use : Betamethasone 2 doses 24 hours apart or dexamethasone 4 doses 12 hours apart
 - Precaution: monitor for hypoglycemia in newborn
 - Value :significantly reduce RDS, NEC and intracranial hemorrhage
- Control Risk factors e.g. maternal diabetes
- Expert Resuscitation
- Early alveolar Recruitment by immediate use of *nasal CPAP*
- Early administration of surfactant

Treatment of RDS

A. Supportive measures

- Incubator care in NICU and Respiratory support (See Before)
- Temperature : goal core temperature = 36.5 – 37 C
- Nutrition :
 - Start with glucose 10 % and aminoacids (in extremely prematures) at rate of 65-75 ml /kg; increase gradually over the first week to 150-180 ml/kg ; avoid overhydration that may open ductus arteriosus
 - Electrolytes added at 2-3rd day
 - Monitor electrolytes and urine output

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Respiratory Support

Aim:

- Keep arterial oxygen pressure between 50 and 70 mm Hg
- The currently recommended range of oxygen saturation targets is 91-95%.

I. Ambient /head box /nasal cannula / Vapotherm

If baby looks comfortable with good saturation and good blood gases (pH >7.25 and PCO₂ < 50 mmHg)

II. Nasal Continuous Positive Airway Pressure (nCPAP)

- Recruits and prevents collapse of surfactant-deficient alveoli
- Early use of CPAP for stabilization of at-risk preterm infants beginning as early as in the delivery room reduces ventilatory needs
- Considered if oxygen saturation cannot be kept > 90% at inspired oxygen concentrations of 40-70% or greater
- Another approach is to intubate the preterm infant, administer intratracheal surfactant and then extubate the infant and begin CPAP.
- If an infant with RDS undergoing CPAP cannot keep oxygen saturation >90% while breathing 40-70% oxygen, assisted ventilation and surfactant are indicated



III. Endotracheal intubation (and Surfactant) and Mechanical Ventilation

- Consider for any of the following
 - Baby unwell, marked recessions
 - No improvement on CPAP :CPAP of 5-10 cm H₂O cannot keep oxygen saturation > 90% while breathing 40-70% oxygen
 - Infants with respiratory failure
 - Arterial blood pH <7.20
 - Arterial blood PaCO₂ of ≥ 60 mmHg
 - Arterial blood PaO₂ of < 50 mmHg



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IV. Surfactant

- Prophylactic treatment
 - Indicated for very low birth weight < 30 weeks
 - In the first few minutes of life before clinical or radiologic confirmation of RDS
- Rescue treatment
 - For babies ≥ 30 weeks
 - Surfactant administered to ventilated infants with clinical and or radiological signs of RDS

Types

- Natural

Suvanta (Bovine surfactant)	<ul style="list-style-type: none"> ○ 4mL/kg (100mg/kg) ○ Repeated if necessary every 6h (up to 4 doses)
Curosurf (Porcine surfactant)	<ul style="list-style-type: none"> ○ Initial dose 2.5mL/kg (200mg/kg) ○ Followed if necessary by 1.25mL (100mg)/kg after 12 hours and 24hours
- Synthetic: Surfaxin which mimic human surfactant

Protocol

- Injected intra tracheal via endotracheal tube
- Observe the baby and ventilator settings closely for 30 minutes after the dose
- Repeat blood gases after 30 minutes
- Avoid EET suction for 1-4 hours if possible
- Consider subsequent doses if
 - Baby has high or increasing ventilator parameters after the 1st dose
 - $FiO_2 > 30\%$ despite adequate ventilator parameters

Side effects

- Bradycardia and desaturation
- Pulmonary hemorrhage
- Air leaks ; Pneumothorax

B. Antibiotics

- Start antibiotics in all infants who present with respiratory distress at birth after the sepsis screen have been obtained.
- Discontinue antibiotics after 2-5 days if blood cultures are negative and no maternal risk factors found

Complications of RDS

Disease related

- Patent ductus arteriosus (PDA) and heart failure
- Intraventricular hemorrhage (IVH)

Treatment related e.g.

- Bronchopulmonary dysplasia (BPD)
- Retinopathy of prematurity (ROP)

Prognosis: Inversely proportionate to gestational age.

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الدفعة الـ 14

Transient Tachypnea of Newborn

- Commonest self-limited respiratory distress in full term
- Due to delay in clearance of fetal lung liquid

Risk factors

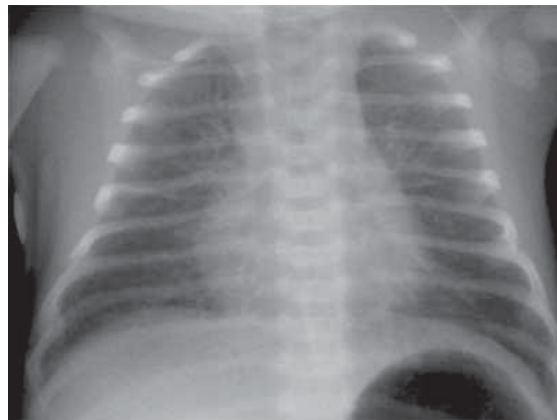
- Cesarean section
- Maternal asthma and smoking
- Maternal diabetes
- Maternal excess analgesia
- Perinatal asphyxia

Clinical picture

- Mild respiratory distress (tachypnea) within few hours after birth.
- The chest generally sounds clear without rales or rhonchi ("quiet" tachypnea)
- Spontaneous resolution usually occur within 72 hours

Chest X-ray

- Prominent perihilar streaking, which correlates with the engorgement of the lymphatic system with retained lung fluid
- Fluid in the fissures
- Hyperinflated lung& mild cardiomegaly



Treatment

Supportive care as before

- 1- Provide oxygen as needed
- 2- Antibiotics
- 3- Infants with significant distress have poor bowel motility and require IV fluids

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Meconium Aspiration Syndrome

- Meconium-stained amniotic fluid (MSAF) occurs in about 15 % of deliveries
- Not all neonates with MSAF develop meconium aspiration syndrome (MAS)
- MAS occurs only in 5 % of infants with MSAF

Pathophysiology

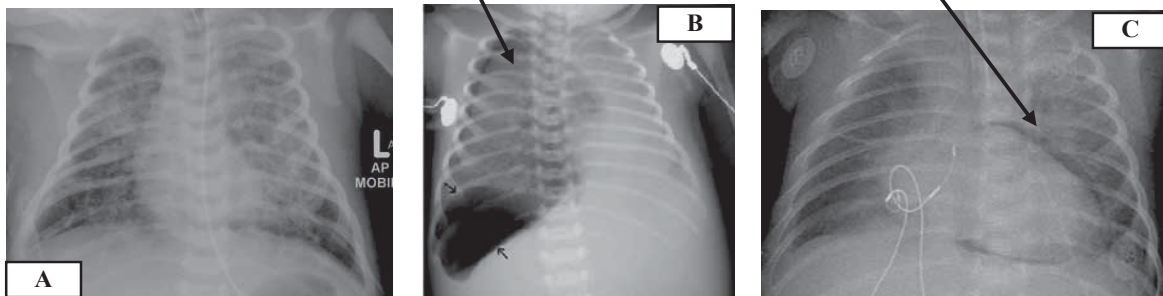
1. Factors that promote the passage of meconium in utero include the following:
 - Perinatal asphyxia
 - Oligohydramnios
 - Maternal infection/chorioamnionitis
2. Meconium may be aspirated before, during, or just after birth
3. Outcome of meconium aspiration:
 - Complete airways obstruction → Patchy collapse
 - Incomplete airways obstruction → Air trapping.
 - Secondary infection & chemical pneumonitis → Surfactant dysfunction
 - Pulmonary hypertension

Clinical picture

- MAS occur typically in term and post-term infants
- Skin, nails and umbilical cord may be meconium stained
- Signs of severe respiratory distress with grunting and cyanosis
- Barrel chest in the presence of air trapping
- Auscultated rales and rhonchi (in some cases)
- May have signs of neonatal encephalopathy

Chest radiograph

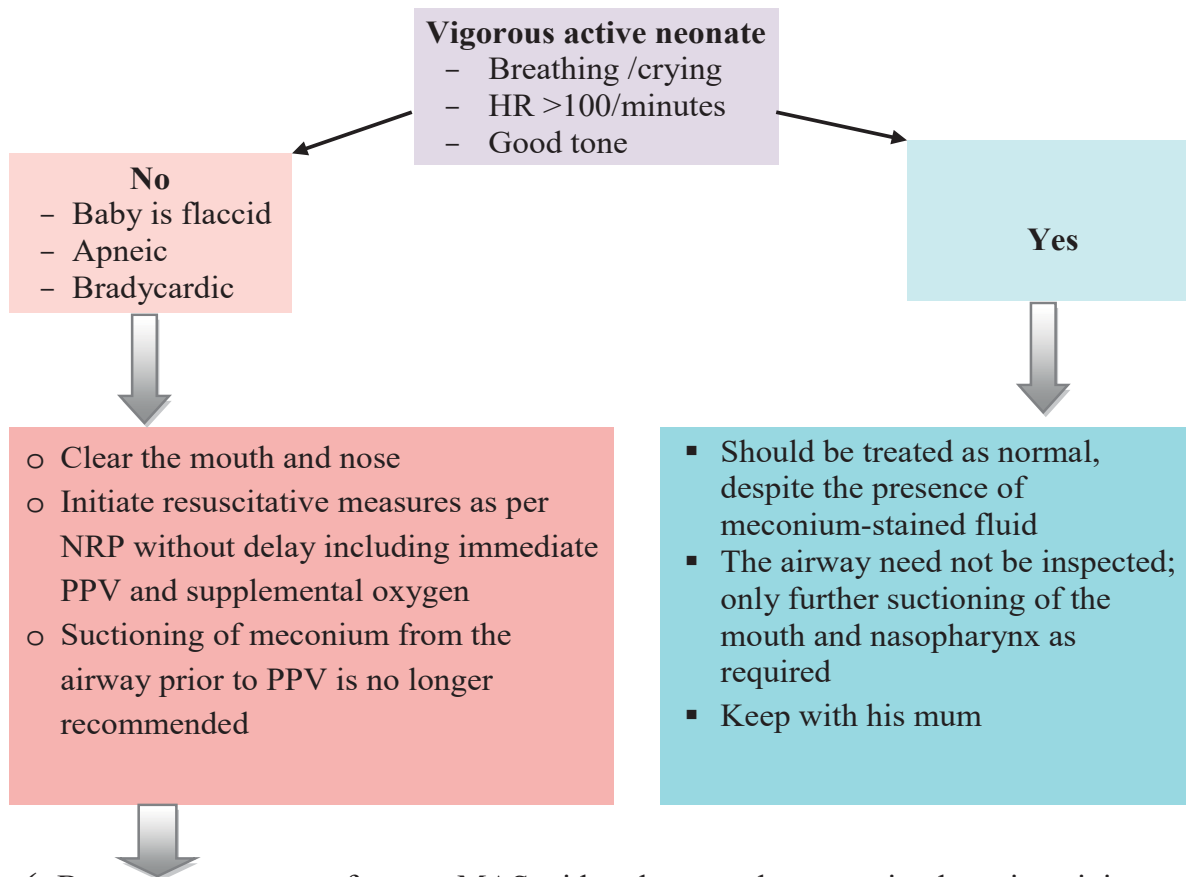
- Hyperinflated chest with patchy consolidations and collapse (A)
- May be air leak e.g. pneumothorax (B) , pneumopericardium (C)



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Management

A. management of meconium stained baby in the delivery room



- ✓ Because most cases of severe MAS with pulmonary hypertension have its origin utero, resuscitative efforts shouldn't be delayed with attempts to clear the airway. So, Routine tracheal suctioning is no longer recommended
- ✓ Intubation and suction only if the airway is obstructed

B. Treatment of MAS

- Respiratory support in NICU as before
- Consider early conventional mechanical ventilation (high oxygen, high rate, long expiratory time, low pressures, use sedation)
- Antibiotics
- Surfactant
- High frequency ventilation for conventional ventilation failure
- Extra Corporeal Membrane Oxygenation (ECMO) for severe MAS

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Neonatal Cyanosis

Definition

- Bluish discoloration of skin and mucus membranes due to presence of more than 5 gm/dl reduced hemoglobin in capillary blood.

Causes

1. Peripheral: with e.g. shock, hypothermia and acrocyanosis

2. Central

A. Pulmonary e.g.

- Severe RDS
- Severe MAS
- Congenital diaphragmatic hernia

B. Cardiac

Congenital cyanotic heart diseases (CCHD) e.g.

- Transposition of great arteries
- Tricuspid atresia
- Tetralogy of Fallot
- Total anomalous pulmonary venous return

C. Hematologic

- Polycythaemia
- Methemoglobinemia (congenital or acquired)

Differential diagnosis

1. Cardiac causes → Emergency echocardiography

2. Hyperoxia test

Differentiate between pulmonary & cardiac causes of cyanosis if emergency Echo is not readily available

- Perform arterial blood gases in room oxygen then give 100% O₂ and perform arterial blood gases again
- If PaO₂ become > 150 mmHg after 100% O₂ → pulmonary cause of cyanosis.
- If PaO₂ remain below 100 mmHg despite 100% O₂ → cardiac cause of cyanosis; These patients should receive PGE1 infusion to maintain ductus arteriosus patent.

3. Blood examination → for polycythemia & methemoglobinemia

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Neonatal Apnea

Definition

- Pauses in breathing for > 15 seconds
- Apnea > 20 second is associated with bradycardia and desaturation

Etiology

1. Apnea of prematurity: causes

- Central (40%) : due to immaturity of respiratory centers
- Obstructive (10%) ; upper air way obstruction e.g. neck flexion
- Mixed (50%)

2. Systemic diseases

- Sepsis
- GORD
- Anemia /polycythemia
- Intra ventricular hemorrhage (IVH)
- Electrolyte disturbances /hypoglycemia
- Hypothermia
- Drugs e.g. sedation, prostaglandins
- Disorders e.g. RDS, PDA, NEC, Pierre – Robin sequence

Treatment

- Investigate and treat any possible underlying cause e.g.
 - Full sepsis screen and start broad spectrum antibiotics
 - GORD: ensure correct NG tube position, positioning the baby with head up tilt, prone or lateral, reduce feed volume and increase frequency, feed thickener and anti GOR medications
- Cardio respiratory monitoring
- Apnea chart to document frequency and severity of apnea.
- Interventions for apnea with bradycardia and desaturations:
 - Tactile stimulation
 - Supplemental oxygen
 - Gentle oral suction
 - Positioning: to avoid extreme flexion or extension of the neck
 - Respiratory stimulants: started in the 1st few days of life for those <30 wks
 - Aminophylline
 - Caffeine citrate
 - BiPAP(Biphasic Positive Airway Pressure) or SiPAP(Synchronized Positive Airway Pressure)
 - Mechanical ventilation if drugs fail.

Self assessment quiz

Case 16

This is a 29 week baby is brought to the neonatal unit. He was born in good condition requiring minimal resuscitation and is put on to nasal CPAP in 25 % oxygen. Over the next four hours, his condition deteriorates. Oxygen requirement increases. There is obvious recession and he is having recurrent apneas. A capillary gas at this point shows mixed acidosis

- a. What is the most likely diagnosis?
- b. What are the 3 appropriate actions you should consider?
- c. What does his chest x ray show?



Case 17

A 3-day-old, 790-g female infant had been ventilated for respiratory distress syndrome and was being weaned effectively from the ventilator. Today she is noted to have an active precordium, bounding pulses, and hypoxia with hypercarbia.

- a. What are the 2 most important investigations urgently needed?
- b. What are the 3 most important differential diagnoses?

Case 18

A term 3500-g female delivered by cesarean section develops a respiratory rate of 70 breaths/min and expiratory grunting at 1 hour of life. She has good tone, good color, and a strong suck.

- a. What is the most likely diagnosis?
- b. What are the 3 most important actions you should do?

Case 19

A girl is born via cesarean section to a 34-year-old mother whose pregnancy was complicated by hypertension and abnormal fetal heart monitoring (cardiotocogram;CTG). At delivery she is covered in thick, green meconium and is limp, apneic, and bradycardic. **What is the appropriate action plan?**

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Abnormal Gestational Age And Birth Weight

Definitions



- **Full term:** Infant born between 37-42 weeks gestations regardless to his weight



- **Premature (pre term):** Infant born < 37 weeks gestations regardless to his weight



- **Postmature (post term):** Infant born > 42 weeks gestations regardless to his weight
- **Small for date (small for gestational age or intra uterine growth retardation):**
Infant with birth weight < 10th percentile of expected from his gestational age.
- **Appropriate for date:**
Infant with birth weight between 10th and 90th percentile of expected from his gestational age.
- **Large for date (Large for gestational age; macrosomia):**
Infant with birth weight > 90th percentile of expected from his gestational age.

Low Birth Weight infants (LBW)

- Any newborn with birth weight less than 2.5 Kg
- Includes:- Premature & Small for Gestational Age
- If birth weight < 1500 grams it is Very Low Birth Weight (VLBW)
- If birth weight < 1000 grams it is Extremely Low Birth Weight (ELBW)

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Small for gestational age (SGA)

Alternative Names:

IUGR (Intra uterine growth restriction or Intra uterine growth retardation)

Infant with birth weight < 10th percentile of expected from his gestational age

Causes

Fetal causes	Maternal causes
<ul style="list-style-type: none"> - Onset usually in the 1st trimester - Usually symmetric IUGR ;weight, length and head are all <10th centile - Fetal anomalies common 	<ul style="list-style-type: none"> - Onset usually in the 2nd -3rd trimester - Usually asymmetric IUGR (Head sparing) - Fetal anomalies less frequent
<ul style="list-style-type: none"> - Congenital infections. - Chromosomal disorders - Multiple congenital anomalies 	<ul style="list-style-type: none"> - Maternal malnutrition and poor health - Placental insufficiency - Maternal smoking or drugs

Clinical Features

- Alert, active & hungry unlike the hypo activity of premature
- Good crying and suckling power
- Low weight (Head may appear large relative to the body)
- Loose, dry, scaling skin with little subcutaneous fat
- Little muscle mass in the limbs and trunk
- Liable to intrauterine distress → Meconium staining

Complications

- Perinatal asphyxia
- Meconium aspiration
- Pulmonary hemorrhage
- Hypoglycemia, hypocalcemia and hypothermia
- Polycythemia and hyper bilirubinemia

Management

Antenatal (if IUGR suspected)

- Repeat fetal ultrasound assessments as often as 1-2 times per week
- Doppler blood flow studies (umbilical artery, umbilical vein, fetal aorta and cerebral arteries)
- Assessment of amniotic fluid volume (amniotic fluid index)
- Cardiotocogram (CTG) assessment; may be daily

Natal/Postnatal

1. Consider early delivery based on the above assessments and gestation
2. Consider antenatal steroids
3. Expert resuscitation as per neonatal life support guidelines
4. Neonatal care as before
5. Encourage Early and frequent feeding
6. Anticipate and manage hypoglycemia, hypocalcemia and polycythemia

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Prematurity

Features of preterm baby

1. Clinical picture of preterm

- Birth weight: < 2.5kg (except infant of diabetic mother).
- Birth length: < 47 cm (except infant of diabetic mother).
- Head circumference: < 33cm.
- Chest circumference: < 30 cm.
- Scalp hair: fine and woolly.
- Skin:
 - Thin, pink, shiny, with little subcutaneous fat
 - Covered with lanugo hair(fine hair present on infants of 24 to 32 weeks' gestation).
- Nails: Don't reach the finger tips.

2. Physical appearance: help in assessing gestational age:

- Ear → shapeless and soft (immature ear cartilage).
- Breast nodule → < 3mm diameter (or even No breast tissue palpable).
- External genitalia → Female: prominent clitoris, labia majora widely separated, labia minora protruding
→ Male: scrotum smooth, no testes in scrotum
- Sole creases → don't reach beyond the anterior 2/3rd of sole (or even absent).

3. Physiological features

- Activity: Weak crying and activity, hypotonic with frog leg posture.
- Hearing
- Startles to loud noise
- Cry: Faint
- Sucking and swallowing: uncoordinated
- Physiological jaundice:
 - Delayed (after the 3rd day)
 - Prolonged (for 2weeks)
 - Deeper (up to 15 mg/dl).

4. Growth

- Preterm infants have rapid growth.
- Preterm infants at 28 weeks' gestation double their birth weight in 6 weeks and treble it in 12 weeks

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Complications of prematurity

Respiratory

Problem	Etiology
○ Respiratory distress syndrome	- Surfactant deficiency
○ Apnea of prematurity	- Immature respiratory centre - Weak chest wall Pliable
○ Air leaks e.g. pneumothorax	- Positive pressure ventilation
○ Aspiration syndromes	- Hypoactive gag and cough reflexes
○ Bronchopulmonary dysplasia	- Prolonged oxygen therapy/ventilation

Cardiovascular

Problem	Etiology
○ Patent ductus arteriosus	- Fluid overload
○ Heart failure	- Fluid overload - PDA
○ Hypotension	- Impaired water and electrolytes regulation

Neurologic

Problem	Etiology
○ Kernicterus	- Immature blood brain barrier
○ Intraventricular hemorrhage	- Fragile ,pressure passive cerebral blood vessels - Fluctuations in blood pressure
○ Hypoxic-ischaemic encephalopathy	- Many risk factors
○ Retinopathy of prematurity	- See later
○ Sensineural deafness	- Late sequel to perinatal asphyxia

Hematologic

Problem	Etiology
○ Anemias	- Frequent sampling - Defective stores e.g. iron,folic,...
○ Coagulopathy /DIC	- Defective coagulation factors

Gastro intestinal

Problem	Etiology
○ NEC	- See before
○ Gastro oesophageal reflux disease(GORD)	- Weak cardia , ↓ gastric capacity and hyperactive pyloric muscles
○ Poor weight gain	- Poor suckling, swallowing and digestion and absorption

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Nutritional

Problem	Etiology
○ Osteopenia of prematurity	– Phosphate deficiency
○ Rickets	– Vitamin D and calcium deficiency
○ Malnutrition	– High growth rate – Poor suckling, swallowing and digestion and absorption – Little subcutaneous fat

Renal

Problem	Etiology
○ <u>More prone to</u> – Dehydration – Metabolic acidosis	– Immature renal functions : – ↓ capacity of urine concentration – ↓ capacity of acid formation

Metabolic

Problem	Etiology
○ <u>More prone to</u> – Hypoglycemia – Jaundice	– Little glycogen stores – Immature hepatic enzymes

Immunologic

Problem	Etiology
○ <u>More prone to</u> – Neonatal sepsis – Neonatal meningitis	– Deficient humoral & cellular immunity – Decreased transplacental antibodies – Deficient physical barriers – Invasive techniques as exchange transfusion / catheterization / intubation

Temperature control

Problem	Etiology
○ Hypothermia	– Little subcutaneous fat – Immature heat regulating center – Large surface area relative to weight → excess heat loss

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Management of prematurity/SGA

Prenatal management

- Induction of fetal lung maturity by prenatal steroids for VLBW and ELBW
- Consider prenatal transfer to a higher center

Delivery room management

Resuscitation

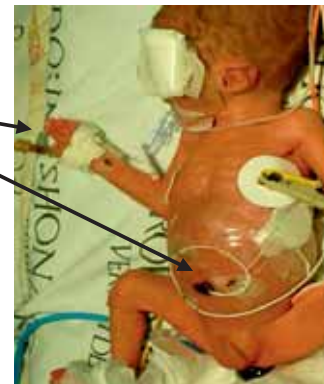
- Resuscitate as usual very gently (see before)
- Keep dry and warm; plastic bags may be used
- Consider nasal CPAP very early
- Consider ET tube insertion if <28 weeks (oral distance = 6+ (wt in kg))
- Give surfactant if
 - Intubation was required in resuscitation
 - Preterm require > 40% oxygen to keep saturation >90% for 15-30 minutes



NICU management

Initial

- Venous access (UVC), and arterial line
- Start glucose infusion
- Give vitamin K 0.5 mg IM or IV
- Start empiric antibiotics after cultures and swabs
- Respiratory support : Early CPAP, surfactant and respiratory monitoring
- Circulation support



Further care

1. Thermoregulation and skin care

2. Fluids balance

Amount

- On the 1st day of life, 60-80ml/kg (90 ml/kg if VLBW)
- Advance by 20 ml/kg per day to a maximum of 150-180 ml/kg per day.
- Adjust up and down according to the infant's clinical condition, plasma sodium, urine output(normal=1-3ml/kg/hour) and daily weight change

Type

- Dextrose 10% (or 5% in ELBW)
- Check electrolytes and calcium at 12-24 hours of age
- Electrolytes added after 24 hours of age, when urine output is adequate
- Basal needs are sodium is 2-3 mEq/kg/d, potassium 1-2 mEq/kg/d, and calcium 45 mg/kg/d (elemental calcium).

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3. Nutrition

A. Total Parenteral Nutrition (TPN)

- I.V. administration of all nutrients (fats, carbohydrates, proteins, vitamins and minerals) necessary for metabolic requirements and growth while awaiting attainment of adequate enteral intake
- Given via peripheral vein, UVC or peripherally inserted central catheter(PICC)
- Calories
 - Start with 50 kal/kg/day
 - Increase slowly to 90-100 kal/kg/day by day 5 – 7 of life
 - Energy targets (*kcal/kg/day*): 120 for premature , 140 for IUGR
And 100 in term infants (Concise pediatrics)

• Macronutrients

	Glucose	Protein	Lipid
Start	4-6 mg/kg/min	2-3 gm/kg/day	2 gm/kg/day
Start day	1 st day	1 st day	1 st day
Advance by	0.5-1 mg/kg/min	1 gm/kg/day	0.5 gm/kg/day
Maximum	12 mg/kg/min	3.5-4 gm/kg/day	3gm/kg/day
Monitoring	Blood glucose	Blood urea nitrogen	Serum triglycerides
Caloric share	50 %	10 %	40%
Preparation	D5% for <1kg D10% for >1 kg Concentrations > 12.5% ;use central line	Aminovenous 10% (1 grams/10ml) Aminosyn-PF TrophAmine	Intralipid 20% (2gram/10ml) <i>More phospholipids</i> Intralipid 10% (1gram/10ml)

(Manual of neonatal care 2017)

- Micronutrients
 - Water soluble vitamins (Soluvit)
 - Lipid soluble vitamins (Vitalipid 4ml/kg/day added to intralipid)
 - Phosphate(Glycophos)
 - Trace elements

B. Enteral feeding

○ Avoid in

- Babies on pressors e.g. Dopamine
- Hemodynamically significant PDA requiring indomethacin or ibuprofen or surgical closure
- Sepsis/suspected sepsis
- Abnormal GIT examination or large/green residuals

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- Enteral feed choice
 - Mother's Breast milk plus fortifiers or premature formula
- Route
 - Nasogastric tube(NGT) until 35-36 weeks of age
 - Large preterm >35weeks can be fed by suckling
- Plan
 - Trophic feeding (minimal enteral feeding)
 - Started at 48 hours for 3 days
 - Amount: 1 mL q 2- 4 hrs.
 - Precautions:
 - a) Feeds should be stopped only if there are signs of intolerance ; abdominal distension, significant vomiting, bilious aspirates or if NEC is suspected.
 - b) Recommence after 4-6 hrs as symptoms resolve
 - Nutritional feeding
 - Started on day 5 or at 48 hours for stable babies > 1kg (When it is clear that minimal enteral feeds are tolerated)
 - Amount :1- 2mL q 3 hrs
 - Feeding advance: 1mL q 8 hrs



C. Nutritional supplements (mainly for those born at <34 wks gestation)

- Multivitamin drops
 - Started by 2 weeks of age (or at start of enteral feeds if later)
 - Orally, once daily for up to 1yr
 - Vitamin D 1000 IU/day, Folic acid 1 mg/day, Vit E 6-8 IU/day
- Iron
 - Begin by 2-4 weeks of life when enteral feedings are tolerated
 - Dose 2-4 mg elemental iron/kg/day until 6 months corrected age

4. Identify and treat complications e.g.

a. Episodes of apnea and bradycardia and desaturation

- Exclude an underlying cause.
- Caffeine citrate
- CPAP is often necessary

b. Intraventricular hemorrhage

- Usually occur within the first 72 hours of life
- Common in those with perinatal asphyxia and severe RDS
- Management (see before)

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c. Patent Ductus Arteriosus (PDA)

- May be asymptomatic
- May cause
 - Apnea and bradycardia
 - Increased oxygen requirement
 - Difficulty in weaning the infant from artificial ventilation
 - Bounding pulse , basal systolic murmur and heart failure
 - Echocardiography is diagnostic
- Management (for symptomatic infant)
 - Avoided by careful fluid balance
 - Restrict current IV fluids
 - Pharmacologic closure with indomethacin or ibuprofen
 - Surgical ligation if pharmacologic closure fail

d. Retinopathy of prematurity (Retro-lental fibroplasia)

Definition

- Retinal vascular proliferation which may progress to retinal detachment, fibrosis and even blindness

Risk factors

- All babies < 1500 g birth weight or < 32 weeks' gestational age
- Exposed to uncontrolled high concentrations of oxygen (controversial)

Clinically

- No warning signs, so screening of babies at risk is mandatory
- Often gradually occurring astigmatism, retinal detachment , and amblyopia



Management

Preventive

- Screening of babies at risk is before discharge, and at 3 months of age
- Lowest O₂ for the least duration if O₂ therapy is indicated (controversial)

Curative

- Laser therapy
- Follow up the affected babies at 6 months intervals

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e. Bronchopulmonary dysplasia (BPD) /Chronic Lung Disease

- Infants who are oxygen dependent at a post-menstrual age of 36 weeks
- Lung damage is due to pressure and volume trauma from artificial ventilation, oxygen toxicity and infection.
- Chest X-ray :shows widespread areas of opacification, sometimes with cystic changes
- These babies are more susceptible to recurrent wheezing, severe bronchiolitis and chest infections

f. Neurodevelopmental problems

High incidence of

- Cerebral palsy
- Delayed language development
- Sensorineural hearing loss and visual impairment.

Discharge from incubator

a. Criteria for discharge

- Infant > 1800 grams with good suckling.
- Adequate oral feeding (can tolerate 150 ml/kg per day)
- Maintain his temperature outside the incubator
- Normal vital data outside the incubator.
- No critical illness nor abnormal lab findings
- Infants with mild BPD may be discharged home on home oxygen therapy with nasal cannula

b. Make notes for

- Clinical examination with discharge weight and head circumference
- Discharge summary and discharge medications prescribed

c. Instructions to the parents:

- Keep infant away from infection ; minimize handling and over crowding
- Schedule for feeding
- Schedule follow up visits to monitor growth, feeding and neurodevelopment and vaccination (according to chronologic age)
- Advice given to parents regarding how and when to seek medical advice

d. Some babies require arrangements for:

- Hearing screening
- Screening for retinopathy of prematurity
- Hip ultrasound e.g. if family history of developmental hip dysplasia or breech delivery (usually done at 4 weeks of age)

Postmaturity

Definition

Infant born after 42 completed weeks of gestation, as calculated from the mother's last menstrual period, regardless of weight at birth

Causes

- Unknown in most cases.
- High incidence with trisomies or anencephaly.

Features

(Most features are due to placental insufficiency)

- Face : opened eye and alert baby
- Skin : pale, wrinkled, peeling, no lanugo hair \pm meconium staining.
- Nails : long nails.
- Weight : average or decreased
- Normal length and head circumference



Complications

- Perinatal asphyxia \pm Meconium aspiration syndrome
- Hypoglycaemia (depleted glycogen stores).
- Polycythaemia
- Hypocalcaemia.
- Persistent pulmonary hypertension

Prognosis

When delivery is delayed 3 wk or more beyond term, mortality is significantly increased; approximately 3 folds as for full term

Neonatal Hypoglycemia

Definition

- In neonates; there is no consensus about blood glucose level below which hypoglycemia is defined
- Practical definitions (not evidence based)
 - In the first 24 hours: blood glucose < 40 mg/dl (2.2 mmol/l)
 - Above 24 hours after birth: blood glucose < 45 mg/dl (2.5 mmol/l)
- WHO recommends keeping blood glucose > 47 mg/dl (2.6 mmol/l)

(Neonatal Emergencies, Harvard University, 2010)

Risk factors for hypoglycemia

1. Increased demand or decreased supply

- Small for gestational age
- Preterm
- Perinatal asphyxia
- Polycythemia
- Hypothermia
- Neonatal sepsis

2. Hyperinsulinism e.g.

- Large for gestational age e.g. Infant of diabetic mother
- Hemolytic disease of newborn
- Beckwith Wiedemann syndrome

3. Endocrinopathy

- Growth hormone deficiency
- Congenital adrenal hyperplasia

4. Inborn errors of metabolism

- Glycogen storage disease
- Galactosemia
- Organic acidemia
- Fatty acid oxidation defects

Clinical Picture

1. Asymptomatic: common presentation
2. Symptomatic:

- Jitteriness	- Apneic episodes
- Tachypnea	- Lethargy or floppiness, poor feeding
- Pallor	- Cyanosis
- Weak or high-pitched cry	- Convulsions or eye-rolling

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Management

Routine screening and monitoring of blood glucose is recommended only for infants who have risk factors or who have clinical manifestations

1. Asymptomatic high risk babies

- Keep warm
- Feed early (within 1 hour of birth) and if enteral feeding contraindicated start glucose 10% (D10%) infusion
- Glucose screening 30 minutes after the first feed
- If low despite feeding, give D10% bolus of 2-4 ml /kg IV
- Monitor blood glucose before 2nd, 3rd, 4th feeds and until at least 2 consecutive normal blood glucose
- If the baby is already on IVF, ensure that glucose intake is appropriate

Glucose intake (mg/kg/min) = fluid rate (ml/hr) × % glucose / 6 × weight (kg)

- In term = 3-5 mg/kg/min
- In preterm = 4-6 mg/kg/min
- In SGA = 6-8 mg/kg/min

2. Symptomatic

- Immediate D10% bolus 2- 4ml/kg followed by continuous D10% IV infusion
- If hypoglycemia persists; ↑ glucose infusion rate steadily up to 10-12 mg/kg/min
- If hypoglycemia persists; add hydrocortisone 2.5 mg /kg 6hourly
- Monitor blood glucose frequently until stable



A. Blood glucose stable ≥ 50 mg/dl for 24 hours

- Withdraw hydrocortisone slowly
- Taper the infusion gradually and advance feeding



B. Consider hyperinsulinism if glucose infusion rate ≥ 12 mg/kg/min

- Workup include: Hypoketotic hypoglycemia with increased c peptide
- Drug options: Glucagon ,Diazoxide, Somatostatin analogue



C. Persistent hypoglycemia

- Investigate for endocrinopathy
- Investigate for inborn errors of metabolism

N.B: - Blood glucose results <40 mg/dl should be confirmed in the laboratory
 - Dextrose concentration > 12.5% should be given via a central venous line

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Infant of diabetic mother

Definition

- Neonate born to diabetic mother (Frank or gestational diabetes mellitus).

Features

- Commonly delivered preterm with ↑ birth weight (Large for gestational age)
- Plump with puffy plethoric facies

Why?

Maternal hyperglycemia → fetal hyperglycemia → increase fetal hepatic glucose uptake, glycogen synthesis & enhance lipogenesis & protein synthesis → macrosomia (increased growth of all organs except for the brain)



Common problems

2. Metabolic

- Hypoglycemia (in 25 %) due to: Maternal hyperglycemia → fetal hyperglycemia → increased fetal insulin production. After birth → interruption of high maternal glucose to the neonate while hyperinsulinemia is going on → hypoglycemia (usually marked after 1-3 hours postnatal)
- Hypocalcaemia & hypomagnesaemia due to: transient hypoparathyroidism
- Hyperbilirubinaemia due to: polycythaemia and reduced RBCs life span
(Both hypoglycemia and hypocalcaemia → jitteriness and seizures)

3. Respiratory

- Respiratory distress syndrome
- Transient tachypnea of newborn

4. Hyper insulinemic features

- Macrosomia may predispose to difficult labor & birth injury
- Transient hypertrophic cardiomyopathy
- Visceromegaly
- Polycythemia (Renal vein thrombosis is common)

4. Congenital anomalies (are 3 fold common, especially)

- Congenital heart diseases
- Sacral agenesis
- Left microcolon
- Neural tube defects

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Management

* Proper control of maternal diabetes and follow guidelines for preterm delivery

* Natal and postnatal

- Delivery room and NICU care
- Treatment of hypoglycemia
 - Encourage early feeding
 - Monitor blood glucose before every feed
 - Manage hypoglycemia as before
- Observe for and manage complications
 - Polycythemia (hydration , partial exchange)
 - Jaundice (phototherapy)
 - Echocardiography if heart murmurs or other signs suggesting congenital heart or cardiomyopathy
- Discharge if no hypoglycemia for 24–48 hours on enteral feeds only and no other complication

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الدفعة ال14

Oesophageal atresia / Trachea Oesophageal Fistula

Definition

- Congenitally interrupted esophagus
- One or more fistulae may be present between the malformed esophagus and the trachea.

Clinical types

			
Type A (10%) Oesophageal atresia without fistula (pure esophageal atresia)	Type B (< 1%) Oesophageal atresia with proximal TOF	Type C (85%) Oesophageal atresia with distal TOF	Type E (4%) TOF without oesophageal atresia (H-type fistula)

Incidence

- 1:3500 live births
- More than half will have additional malformations

History

Antenatal ultrasound sometimes shows

- Polyhydramnios
- Absent stomach bubble
- Associated congenital anomalies

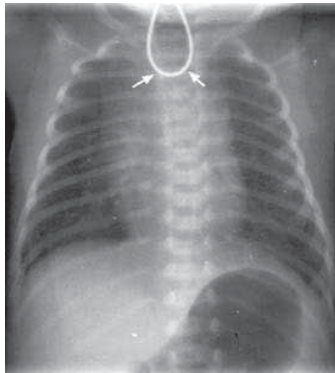
Clinical features

- Excessive production of frothy saliva
- Episodes of choking and cyanosis exacerbated with attempts at feeding
- Failure to pass naso gastric tube

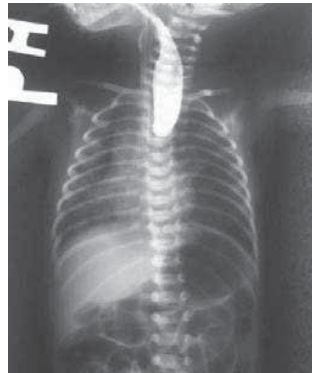
Investigations

- Chest x ray with naso gastric tube in situ reveals tip of tube in the oesophageal pouch ; presence of gas in stomach indicate a fistula
- Barium swallow can detect H type (avoided in atresia; risk of aspiration !!)
- Search for other anomalies by Echo , renal ultrasound ,spine x ray

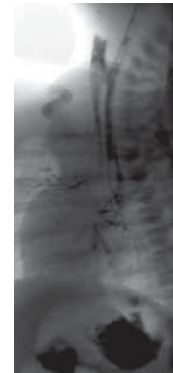
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Plain x ray chest shows curling up of the NGT in the oesophageal pouch



Barium swallow shows barium filled esophageal pouch



Barium swallow shows H shaped TOF

Management

- Nurse head up and prone
- Pass a large bore tube and keep on low level suction to prevent aspiration of secretions
- Transfer to a surgical center when stable for repair

Duodenal atresia

Definition

Congenital discontinuity of the duodenum usually in the region of the ampulla of Vater that leads to bowel obstruction

Incidence

Down syndrome (30%), prematurity and malrotation

Clinical features

- Antenatal history of polyhydramnios
- Bilious vomiting within hours of birth
- Distended stomach
- Delayed passage of and small amounts of meconium

Investigations

- Abdominal x ray :double bubble sign of distended stomach and duodenum
- Blood : electrolytes, glucose and blood gases



Treatment

- Stop enteral feeding, start IVF, and insert nasogastric tube on free drainage
- Correct electrolyte and acid base disturbances
- Transfer to a surgical center when stable for repair

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Benign Neonatal skin disorders

Criteria

- Etiology is unknown in most of them
- Require no treatment
- Fade spontaneously

1. Erythema toxicum neonatorum

- Benign, self-limited, asymptomatic disorder
- Lesions usually begin 24 to 48 hours after birth
- Intense erythema with a central papule or pustule that resembles a flea bite
- The eruption fades spontaneously within 5 to 7 days. No treatment is necessary



2. Transient Neonatal Pustular Melanosis

- Presents at birth with 1- to 2-mm sterile vesiculopustules or ruptured pustules
- Disappear in 24 to 48 hours, leaving pigmented macules with a collarette of scale



3. Neonatal acne

- Multiple, 1- 2-cm ,yellowish-white papules
- Usually located over the nose and cheeks of full-term infants
- It represents a normal physiologic response to maternal androgenic stimulation of sebaceous gland growth



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4. Cutis Marmorata

- Transient, netlike, reddish-blue mottling of the skin caused by variable vascular constriction and dilatation
- It is a normal response to chilling, and on rewarming, normal skin color returns



5. Mongolian spots

- Flat, slate-gray to bluish-black, poorly circumscribed macules.
- They are located most commonly over the lumbosacral area and buttocks
- More in dark skinned infants



Diaper Dermatitis

1. Irritant Diaper Dermatitis

- The diaper area is bathed in urine and stool and occluded by plastic diaper covers
- Failure to change diapers frequently provides time for fecal bacteria to form ammonia by splitting the urea in urine
- Erythema; scaling; and, at times, maceration are usually confined to the convex surfaces of the perineum, lower abdomen, buttocks, and proximal thighs, sparing intertriginous areas



Treatment

- Frequent diaper changes and gentle cleansing
- Lubricants and barrier pastes
- A short course of low-potency steroids may hasten resolution.

2. Candidal Diaper Dermatitis

- A common sequela of oral or parenteral antibiotic therapy
- Bright red eruption, with sharp borders and pinpoint satellite papules and pustules
- Intertriginous areas are involved
- May be with oral thrush



Treatment

- Topical antifungal therapy
- The occasional resistant case may require a brief course of oral medication.

3. Staphylococcal Diaper Dermatitis

- Thin-walled pustules on an erythematous base
- Typically, these rupture rapidly and dry, producing a collarette of scaling around the denuded red base



Treatment

- Oral and topical antibiotics

Examination of newborn

Quick examination

Value: detect life threatening insults

- Apgar scoring \Rightarrow (done at 1, 5 minutes; at 5 minutes is more important).
- Normal newborn is conscious, active, alert
- Color
 - Normal newborn is pinkish in color.
 - Abnormal appearance of the newborn may be:
 - Pallor
 - Plethora
 - Cyanosis
 - Jaundice
- Vital signs
 - Heart rate (120 – 140 beat/minute)
 - < 80 \rightarrow Bradycardia
 - > 180 \rightarrow tachycardia
 - Respiratory rate (\approx 40 /minute)
 - > 60 \rightarrow tachypnea (RD)
 - Temperature (36 – 37.5°C)
 - < 35.5 \rightarrow hypothermia
 - Mean blood pressure (should equal gestational age in weeks)
- After the end of quick examination the newborn will be considered as
 - Normal \rightarrow Proceed to other lines of examination.
 - Abnormal \rightarrow Admit e.g. to NICU

Detailed examination

Measurements

- Weight
- Length
- Head circumference

Regional examination

a- Head

- Anomalies / dysmorphism
- Birth trauma
- Fontanelles

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- Congenital cataract /subconjunctival hemorrhage
- Oral moniliasis

b- Neck

- o Short neck or webbing (Turner).
- o Goitre (enlarged thyroid).

c- Limbs

- o Birth trauma /Malformations.
- o Developmental Hip Dysplasia (DDH)

Risk factors

- o Family history
- o Breech presentation
- o Olighydramnios
- o Congenital myopathies and neurological disease

Screening

- o If risk factor present and newborn examination is normal
- o Hip ultrasound scan at 4-6 weeks
- o Refer to orthopedics only if ultrasound abnormal



Abnormal clinical examination include

- Positive Ortolani s test (Abducting the femur produces a palpable clunk)
- Positive Barlow s test (femoral head pushed more away from acetabulum)
- Asymmetrical gluteal creases
- Limited hip abduction
- Unequal leg length

If hip examination confirmed to be abnormal

- Arrange for early hip ultrasound (Between 2- 4 weeks of life)
- Arrange early orthopedic referral

d- Genitalia

- o Ambiguous genitalia
- o Undescended testis/ Hypospadias

e- Skin

- o Meconium staining skin , nails and umbilical stump
- o Edema (Hydrops fetalis).

f- Urine and stool

- o Normal neonate should pass urine & meconium within 24 hrs of birth

Systemic examination

a- Cardiovascular system

- o Apex beat: Normally in Left 4th space at the mid clavicular line.
- o Murmurs: Most of murmurs in early neonatal period are transient
- o Femoral pulsations: If absent Aortic coarctation is suspected.

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b- Chest examination

- Signs of respiratory distress.
- Apnea.
- Auscultation for wheezes, crepitations,

c- Abdominal examination

- Liver may be palpable 2 cm in neonates
- Check for organomegaly, ascitis, umbilicus,
- Causes of neonatal abdominal masses e.g.:
 - Hydronephrosis.
 - Multicystic – dysplastic kidney.
 - Ovarian cyst.
 - Intestinal duplication.
 - Neuroblastoma.
 - Wilm's tumor.
- Scaphoid abdomen with severe respiratory distress strongly suspect congenital diaphragmatic hernia

d- Neurological examination

- Level consciousness.
- Muscle tone (normally flexed all limbs).
- Neonatal reflexes.(tendon reflexes and primitive reflexes)

Special examination**1. Check for congenital anomalies e.g.**

- Cleft lip
- Tracheo-esophageal fistula
- Limb anomalies e.g. talipes equinus
- Congenital heart diseases
- Imperforate anus.

2. Search of birth injuries e.g.

- Cranial injuries
- Nerve injuries

3. Assessment of gestational age

- From the history (last menstrual period).
- From the ultrasound exam. during pregnancy
 - Biparietal diameter
 - Femoral length
- From physical and neurological assessment: New Ballard Score

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The New Ballard Score

- A set of procedures developed by Dr. Jeanne L Ballard, to determine gestational Age through neuromuscular and physical assessment of a newborn fetus
- Usually done after newborn stabilization

A. Neuromuscular maturity

Score	-1	0	1	2	3	4	5	Sign score
Posture								
Square window (wrist)								
Arm recoil								
Popliteal angle								
Scarf sign								
Heel to ear								



Posture



Arm recoil



Scarf sign



Square window test



Popliteal angle

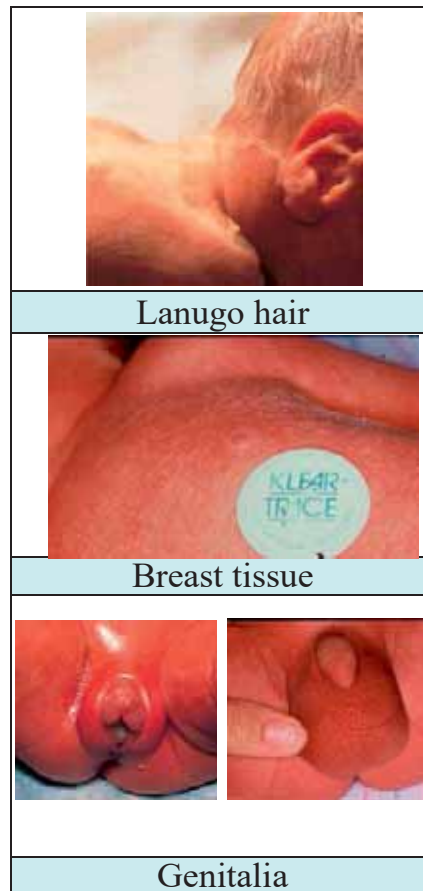
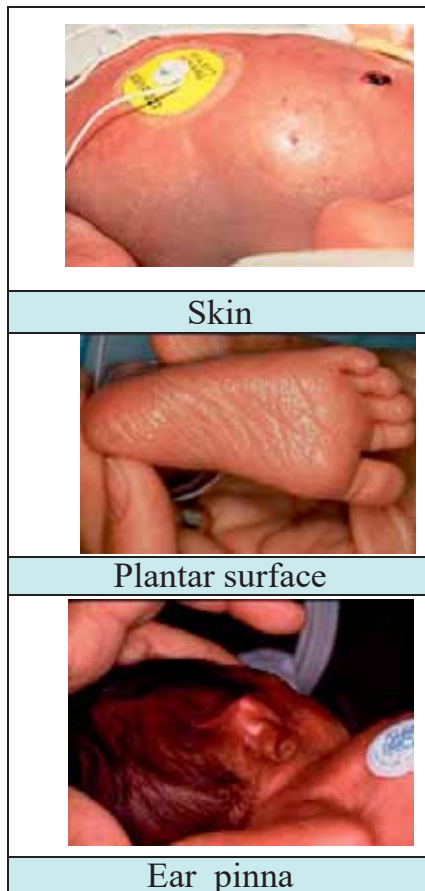


Heel to ear

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B. Physical maturity

Sign	Score							Sign score
	-1	0	1	2	3	4	5	
skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth pink, visible veins	Superficial peeling &/or few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled	
Lanugo	none	Sparse	Abundant	Thinning	bald areas	mostly bald		
Plantar surface	Heel-toe 1:40- 50 mm 2: < 40 mm	> 50 mm no crease	Faint red marks	Anterior transverse crease only	Creases ant. 2/3	Creases over entire sole		
Breast	Imperceptible	Barely perceptible	Flat areola no bud	Stippled areola 1-2 mm bud	Raised areola 3-4 mm bud	Full areola 5-10 mm bud		
Eye /ear	Lids fused 1: loosely 2: tightly	Lids open pinna flat stays folded	Curved pinna; soft; slow recoil	Well-curved pinna; soft but ready recoil	Formed & firm instant recoil	Thick cartilage ear stiff		
Genitals Male	Scrotum flat, Smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae		
Genital Female	Clitoris prominent & labia flat	Prominent clitoris & small labia minora	Prominent clitoris & enlarging minora	Majora & minora equally prominent	Majora large, minora small	Majora cover clitoris & minora		
Total physical maturity score								



Total score	Weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

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Students Notes

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Pediatric life support

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الدفعة الـ 14

Pediatric Basic Life Support (BLS)

- Step by step maneuvers that done by a rescuer to save life of an apparently collapsed victim

1. Safety: of the rescuer and then the victim

2. Stimulate

- Verbal and tactile stimulation.
- Never shake child.
- ☆If the child responds:
 - No need for the Cardio pulmonary resuscitation (CPR).
 - Reassess the case.
- ☆If does not respond: proceed in CPR

3. Shout

- ☆Shout for “help” while remaining with the child.
- ☆ Initiate BLS maneuvers immediately.
- ☆Alert the emergency Medical Services EMS providing the following information:
 - 1- Location of the emergency and telephone number used.
 - 2- Type of accident, severity, and urgency of situation.
 - 3- Number and age of victims.
 - 4- End the phone call only after the controller.

4. Airway

A) Opening the airway:

- secure the airway in the unconscious by one of the following methods:

1= Head=tilt=chin lift:

- ✧ Suitable for all cases except when cervical trauma is suspected.
- Tilt the head back with one hand on the forehead .
- Place the head in neutral position in infants and slightly extended in older child
- Lift the chin upwards with finger tips of the other hand.



2= Jaw thrust maneuver:

- ✧ For suspected cervical injury.
- The hands placed on either side of the child head.
- raise both angles of the child's lower jaw
- Rescuer's elbow should rest on the surface on which the victim is lying.



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B) Checking the air way:

- Look into the mouth.
- Bind finger sweeps must never be performed
- If there is visible foreign bodies that can be removed by one finger sweep the rescuer can try if not, leave it.

5. Breathing

- Check breathing: look, listen and feel (time allowed 10seconds).
- If the child is breathing spontaneously and effectively: reassess.
 - If no spontaneous effective breathing: rescue breathing.
 - Rescue breaths: up to five initial rescue breaths should be attempted, each breath should be slow, 1-1.5 seconds and taking breath inbetween .

Techniques of breath:

1. For infants ⇒ Mouth-to-mouth and nose



2. For children ⇒ Mouth-to-mouth, (nostrils should be closed).

- ✧ If chest movement not seen check position of airway.
- ✧ If despite repositioning of airway, foreign body obstruction is suspected.
- ✧ Once initial rescue breath has been delivered proceed to circulation.

6. Circulation

- The standard method for assessing circulation is feeling effective central pulse.
 - In infants: brachial pulse or femoral pulse.
 - In children: carotid artery.
- Observe signs of circulation “signs of life” as cough, moving or normal breath as not to spend time in feeling pulse.
- If pulse is found or there are signs of life: reassess breathing
- If no effective spontaneous breathing, rescue breaths should be continued at a rate of 20 breaths/min.
- If signs of circulation are absent e.g.:
 - No pulse
 - No signs of life.
 - Pulse is very slow < 60/min, with signs of poor perfusion Or you are totally unsure

Decision⇒ start external chest compressions.

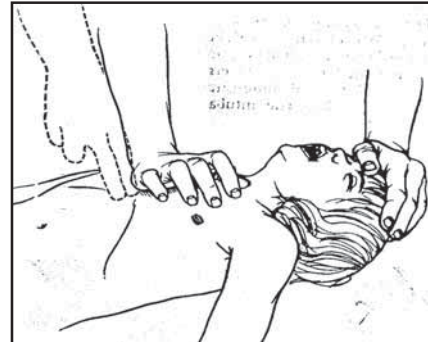
Principles of external chest compression (ECC):

- ✧ Serial rhythmic compressions of the anterior chest wall that causes blood to flow to the vital organs.
- ✧ Place the child supine on a hard flat surface while keeping airway opened.
- ✧ Depress the chest tip approximately 1/3 to 1/2 the antero posterior diameter.



1. In infants:

- Site of compression is one finger breadth below the inter-nipple line
- Use two fingers technique or two thumbs-encircling hands technique.



2. In children:

- Site of compression is one finger breadth above xiphoid process.
- One hand technique is recommended for child <8 years
- In older child (>8 years) use two hands technique.

Compression ventilation ratio:

- In new born ratio of 3/1
- In infants and children ratio of 5/1
- In children > 8 years and adults ratio of 15/2

Reassess

- After one minute CPR delivering, the rescuer should briefly stop to assess the ABC.

Recently, for cases of cardio pulmonary arrest, resuscitation algorithms follow C-A-B: circulation (compressions)-Airway –Breathing instead of traditional A-B-C

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Anaphylaxis

Anaphylaxis

- A serious IgE-mediated allergic reactions
- On exposure to the sensitizing allergen, mast cells and basophils, and macrophages, release a variety of mediators (histamine, **tryptase**) and cytokines that can produce allergic symptoms

Presentation

- The onset of symptoms may vary depending on the cause of the reaction.
- Reactions from ingested allergens (foods, medications) tend to have more gastrointestinal symptoms And delayed onset (minutes to 2 hr) compared with those from injected allergens (insect sting, medications)

Diagnosis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is Fulfilled:

1. Acute onset of an illness (minutes to several hours) with
 - Skin and/or mucosal tissue → Generalized hives, pruritus or flushing, swollen lips/tongue/uvula.
 - **And at least 1 of the following:**
 - a. Airway obstruction by edema: stridor or wheeze/bronchospasm.
 - b. Hypotension, or collapse or syncope
2. **Two or more** of the following that occur rapidly **after exposure to a likely allergen for that patient** (minutes to several hours):
 - a. Involvement of the skin/mucosal tissue (as above)
 - a. Airway obstruction by edema: stridor or wheeze/bronchospasm.
 - b. Hypotension, or collapse or syncope
 - d. Persistent gastrointestinal symptoms (e.g. colic, vomiting)
3. Hypotension following exposure to **known allergen for that patient**

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Management

- ✓ Anaphylaxis is a medical emergency requiring aggressive management
- ✓ Overall principles of management of anaphylaxis include:
 - Look for any allergen and remove/ Check MedicAlertR bracelet
 - Call for help
 - Give high-flow oxygen
 - Rapid cardiopulmonary assessment of ABC.

If a problem is identified with A or B or C, give IM Adrenaline

IV adrenaline should only be given to monitored patient in cardiopulmonary arrest.

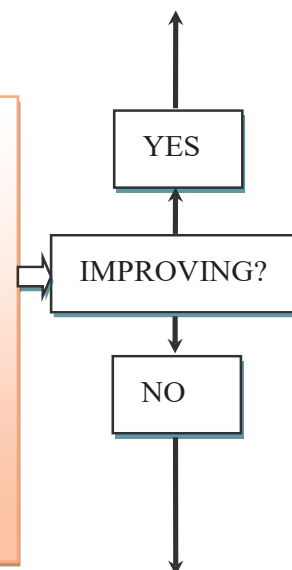
Flow chart for anaphylaxis

1. Define anaphylaxis And signs of allergy
2. Assess ABC
3. **No upper airway compromise nor shock nor wheezing:** → Reassure + oral antihistamines and observe carefully for 4 hours.
4. **No upper airway compromise nor shock but wheezing exists:**
→ Nebulized salbutamol + Oral prednisolone + Oxygen, if needed

1. Observe carefully for 4 hours is mandatory as anaphylaxis may have a biphasic component
2. Reassess for symptom progression
3. Oral antihistamine +/- oral prednisolone
4. Consider adrenaline auto-injector (EpiPen)
5. MedicAlertR bracelet and referral to allergy specialist

5. Upper airway compromise or shock :

1. Call for help: ***Put a pediatric crash call***
2. Apply high flow oxygen
3. Give:
 - IM adrenaline **10 mcg/kg** in antero lateral aspect of thigh
 - Treat shock with 20 mL/kg 0.9% saline
 - Consider nebulized adrenaline
 - Driven by oxygen at 3–5mL of 1:1000 solution
 - If the child still has stridor after the first dose of IM adrenaline



After 5 minutes**Ongoing stridor**

- Repeat IM adrenaline
- Repeat nebulized adrenaline
- Call ENT for artificial airway
- Consider adrenaline infusion in PICU if no response in 3 minutes

On-going shock

- Further 20mL/kg normal saline
- If no improvement after 40mL/kg of fluid, Consider intubation and further IM adrenaline or infusion in PICU

On-going lower airway obstruction

- Consider nebulized salbutamol
- Consider IV hydrocortisone
- Consider aminophylline or salbutamol infusion

Cardiopulmonary arrest during anaphylaxis:

- CPR and PALS measures
- Prolonged resuscitation efforts encouraged (if necessary)
- Consider:
 - Transport to ICU
 - High-dose epinephrine
 - Rapid volume expansion
 - CPR for asystole or pulseless electrical activity

Adrenaline dosage

Drug	Route	Dose	Notes
Adrenaline (1:1000 solution)	IM	10mcg/kg or: <6yrs: 150mcg (0.15mL) 6–12yrs: 300mcg (0.3mL) > 12yrs: 500mcg (0.5mL)	IM adrenaline can be repeated after 5 min if required
	Nebulized	3–5mg (3–5mL of 1:1000 solution) with O2 at 10–15L/ min	Treatment of stridor
Adrenaline (1:10,000 solution)	IV or IO	10mcg/kg	Only for treatment of cardiopulmonary arrest 2ry to anaphylaxis

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Shock

Shock is defined as inadequate perfusion and oxygenation of the body's vital organs

Causes of shock:

Cardiogenic	<ul style="list-style-type: none"> ▪ Myocarditis ▪ Cardiomyopathy ▪ Dysrhythmias ▪ Heart failure 	C
Hypovolaemic	<ul style="list-style-type: none"> ▪ Diarrhea /vomiting ▪ Diuresis ▪ Hemorrhage: external or internal ▪ Burns 	H
Obstructive	<ul style="list-style-type: none"> ▪ Obstructed congenital heart disease (duct dependent systemic flow e.g. severe coarctation, left hypoplastic heart syndrome, interrupted aortic arch) ▪ Tension pneumothorax ▪ Cardiac tamponade 	O
Distributive	<ul style="list-style-type: none"> ▪ Anaphylaxis ▪ Neurogenic ▪ Sepsis especially gram-negative 	K (Kinetic)

Pathophysiology

Inadequate perfusion → failure to supply oxygen and substrate to cells and impaired removal of their waste products → Anaerobic metabolism and tissue acidosis will result.

Compensated shock:

- Reduced blood flow to non-vital organs e.g. **Skin** → decreased capillary refill (> 3 seconds) and cool peripheries. In contrast, patients with “warm” or septic shock can present with warm skin with brisk capillary refill and bounding pulses.
- **Tachycardia** (thready pulse) → to maintain cardiac output. Early sign of shock and is typically apparent well before hypotension, which is a late feature in pediatric shock
- **Tachypnea** → to improve oxygen delivery.
- Activation of renin-angiotensin system conserves water with reduction in GFR → urine output < 1 mL/kg/h (**Oliguria**).
- Blood pressure is maintained. There may be agitation and confusion
- Features suggesting an underlying **Cause** e.g. A gallop cardiac rhythm can indicate heart failure, ongoing body fluid loss, sepsis etc....

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Decompensated shock:

- Failure to treat the cause will lead to further impairing myocardial function and anaerobic metabolism increases
- The resultant reduction in blood flow to the vital organs causes:
 - Reduction of conscious level — coma scale <8, only responsive to pain
 - Hypotension
 - Respiratory failure
 - Anuria

Monitoring**Evaluation for infectious etiology:**

- Sources : Blood, urine, tracheal secretions, CSF, wound, pleural fluid, or stool
- Workups: Stains, cultures, PCR for bacteria, fungus, viruses

Evaluation of organ function

- Pulmonary: Arterial blood gases (ABG)
- Cardiac: ABG, lactate
- Liver: LFTs, coagulation studies
- Renal: BUN, creatinine, bicarbonate, serum sodium
- Hematology: CBC, Evaluation for DIC: PT, PTT, fibrinogen, D-dimer
- Extent of inflammatory state: CRP, WBC, ESR, procalcitonin

Additional studies

- Electrolytes
- Ionized calcium
- Magnesium
- Phosphate

Management of shock**Goals**

The goals of initial management are to restore normal mental status, heart rate and blood pressure, good peripheral perfusion, and adequate urine output.

Precautions

- If compensated shock is suspected, treat promptly and aggressively to prevent progression to decompensated shock.
- All patients require a secure vascular access, oxygen therapy, and cardiopulmonary monitoring. After each intervention, look for improved vital signs, skin perfusion, and consciousness.

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General Care: ABC

- Oxygen (100% by mask or CPAP or endotracheal tube)
- Intravenous access → two large-bore peripheral IV lines or an IO needle
- Basic life support as needed
- Monitoring :
 - Pulse oximetry, ECG, blood pressure
 - Blood glucose testing
 - Monitor urine output (catheter); the goal is 1–2 mL/kg/h

1. Hypovolemic shock

- Infuse a fluid bolus of 20 mL/kg of normal saline (NS) or lactated ringer (LR) as rapidly as possible.
- Several boluses may be required; Typically no more than 60 mL/kg
- Hemorrhagic shock may require blood (10 mL/kg) to replace ongoing losses plus controlling external bleeding

2. Cardiogenic shock

- The diagnosis is suggested by:
 - * History of cardiomyopathy or congenital heart disease
 - * Abnormal cardiac rhythm
 - * Rales, gallop, or friction rub
 - * Hepatomegaly
 - * Chest radiographs may show cardiomegaly and pulmonary edema
- Expert consultation is always mandatory

A. Myocarditis, cardiomyopathy, congenital heart disease

- An initial bolus of NS/LR may be given at volumes of 5–10 mL/kg
- Reassess frequently for signs of cardiac failure
- Inotropes (e.g. dobutamine, dopamine)

B. Brady arrhythmia with poor perfusion

- Cardio pulmonary resuscitation (CPR) if heart rate < 60 /min despite oxygen and ventilation
- If persist :
 - Epinephrine IV 0.01 mg/kg (0.1 ml /kg of 1:10 000)
 - Atropine for increased vagal tone or heart block

C. Tachy arrhythmia with poor perfusion

- **Supraventricular tachycardia**
 - Vagal maneuvers
 - IV line available → Adenosine
 - IV line unavailable or failed adenosine → Synchronized cardioversion (0.5–1 J/kg)

- **Ventricular tachycardia (with pulses)**
 - Stable: Amiodarone or Procainamide
 - Unstable: Synchronized cardioversion (0.5–1 J/kg)
- **Ventricular fibrillation and pulseless ventricular tachycardia:**
 - Defibrillation shock 2 J/kg
 - ↓
 - CPR
 - ↓
 - Defibrillation 4 J/kg
 - ↓
 - CPR
 - ↓
 - Alternate drugs (Epinephrine, then Amiodarone) with defibrillation

3. Obstructive shock

Obstructed CHD	Tension pneumothorax	Cardiac tamponade
<ul style="list-style-type: none"> – PGE1 infusion – Expert consultation 	<ul style="list-style-type: none"> – Needle decompression – Tube thoracostomy 	<ul style="list-style-type: none"> – Fluid bolus 20 ml /kg NS or LR – Pericardiocentesis

4. Distributive shock

Anaphylactic: See anaphylaxis

Neurogenic

- Fluid bolus 20 ml /kg NS or LR
- Vasopressor

Septic shock

- Push repeated fluid boluses unless rales, respiratory distress or hepatomegaly develop
- Correct hypoglycemia and hypocalcemia
- Administer first dose of antibiotic STAT
- Consider STAT vasopressor drip and stress dose of hydrocortisone
- If shock is fluid resistant → Start vasopressors to correct perfusion:
 - Normotensive → Dopamine
 - Hypotensive vasodilated (warm) shock → Norepinephrine
 - Hypotensive vasoconstricted (cold) shock → Epinephrine
 - Consider transfusion to hemoglobin > 10 g/dl, more fluid boluses , and Milrinone

(Pediatric Advanced Life Support, American Heart Association)

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Answers

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الدفعة الـ 14

Growth and development

Case 1

- Absent both tibial and femoral epiphysis (i.e. delayed bone age)
- Congenital hypothyroidism
- Widely open anterior fontanel and open posterior fontanel > 1 cm

Case 2

D

In congenital adrenal hyperplasia, a deficiency of enzyme 21-hydroxylase causes an interruption in the pathway for production of cortisol; the end result is hypersecretion of androgenic precursors and clinical manifestations of virilism and protein anabolism and there is rapid growth in stature, with marked acceleration of osseous maturation. The result is early closure of epiphyses and failure to achieve full growth

Case 3

B

A normal 3-month-old infant can raise his or her face 45° to 90° from the horizontal. Not until 6 to 8 months of age should an infant be able to maintain a seated position

Case 4

C

Infant feeding

Case 1

- lactose intolerance secondary to post gastro enteritis syndrome
Clinical pointers to diagnosis:
 - Persistent diarrhea
 - Peri anal soreness
 - Irritability with distended abdomen
- Laboratory diagnosis
 - Detect reducing substance in stool (lactose)
 - Detect acidic pH of stool (lactic acid)
- Use of lactose free milk for two weeks

Case 2

- A humanized formula
- Feed at 3 hours intervals, so number of feeds about 8/24 hours
- Amount of milk required /feed
 - Age in months X 10 + 100 = 120 ml
 - Amount can be calculated by caloric method as well

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d. Preparation of the formula (concentration of milk given)

i- Formula of dried powdered milks:

- ⊕ One measure of 4 gm diluted by 30 mL boiled water e.g. Liptomil, Nan, Aptamil 1.
- ⊕ One measure of 8 gm diluted by 60 mL boiled water e.g. Similac, S 26.

ii- Formula of fresh fluid animal milk: not preferred at all before 1 year

Case 3

a. Cow milk protein allergy

b. Laboratory test required

- Occult blood in stool
- A Skin prick test or radioallergosorbent test (RAST)
- Therapeutic trial of milk withdrawal is more informative

c. Use of Casein hydrolysate based formula; the best choice

N.B

- Most gastrointestinal manifestations resolve within several days
- Cow's milk in the mother's diet is the most common identifiable cause of food-allergic reactions in nursing infants
- About 50% of infants who experience proctocolitis while nursing improves with removal of cow's milk from the mother's diet

(Nelson textbook of pediatrics)

Case 4

1. Lactose free formula
2. Predigested formula
3. Phenylalanine low formula
4. Lactose free formula
5. Premature formula

Nutrition

Case 1

a. Probable diagnosis; Edematous PCM (mostly Kwashiorkor)

Features suggesting diagnosis:

- Characteristic edema
- Muscle wasting
- Weight /expected weight at 10 months between 60-80% with edema
- Skin changes over buttocks
- Pallor; indicating possible anemia
- Enlarged liver

b. see textbook

Case 2

a. Dietetic Marasmus

b. Possible 4 risk factors

- Exclusive breast-feeding and delayed weaning
- Insufficient breast milk
- Being one of twin; usually have higher growth rates

- Low birth weight

Case 3

a. 3rd degree marasmus secondary to congenital heart disease; ASD

b. Congenital heart disease; ASD

c. Direct your investigations to diagnose the congenital heart disease e.g. echocardiography ,chest x ray and ECG

d. Lines of treatment

- Consult pediatric cardiologist and nutritionist
- Medical
 - Control heart failure (diuretics, digoxin, vasodilators).
 - Dietetic treatment as before
- Interventional/Surgical
 - ASD complicated with growth failure will usually require transcatheter or open heart surgical closure when the baby reaches suitable size for intervention

Case 4

a. Rickets complicated with hypocalcemia tetany

b. See treatment of tetany

Case 5

B

Case 6

E

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Genetics

Case 1

- a. Turner syndrome
- b. See textbook

Case 2

- a. Down syndrome
- b. Duodenal atresia and congenital acyanotic heart disease (likely endocardial cushion defect or VSD)
- c. Place a nasogastric tube and start IV fluids and electrolytes
Treatment of the congenital heart disease
Investigate for and treat jaundice
Surgical consult for a duodenostomy.
- d. An echocardiogram
A karyotype

Case3

Subluxation of the atlantoaxial joint

Case4

- Likely diagnosis is Down syndrome complicated by acute leukemia (acute myeloid leukemia or acute lymphoblastic leukemia)
- Immediate blood film with differential count for blast cells and arrange for bone marrow examination at the first chance

Diarrhea

Case 1

a. **Diagnosis:** Intussusception complicating acute gastro enteritis

b. **Investigations:**

Abdominal ultrasound is the gold standard to diagnose Intussusception

Other important investigations:

- Serum electrolytes
- Blood urea nitrogen and creatinine
- Stool culture
- CBC

c. **Management:**

Correct dehydration and electrolyte disturbances

Consult pediatric surgeon immediately

Case 2

a. Severe dehydration

b. Insert IV line → Take blood sample for investigations (Electrolytes /BUN/ CBC/ Blood gases) → Push 20 ml /kg normal saline IV and watch for improvement of perfusion and mental status

Case 3

a. Moderate (to severe) dehydration

b. ORS is not suitable due to repeated vomiting and being tired

c. Amount of fluids required = 100 ml /kg

Infection

Case 1

- a. Pertussis (baby was infected most likely from his mother)
- b. Confirm diagnosis by nasopharyngeal swab and smear or PCR or culture for B. Pertussis and B. Para pertussis

Case 2

Typhoid fever

Case 3

- a. Typhoid fever
- b. The important 4 lines of treatment including
 - Keep NPO, Intravenous line and intravenous fluids (correct shock then maintenance fluids)
 - Fresh blood transfusion
 - Ceftriaxone IV daily
 - Surgical consultation for possible resection of involved part (Don't forget typhoid fever is a notifiable disease)

Case 4

- a. Neonatal tetanus (tetanus neonatorum)
- b. Picture (a) shows Risus Sardonius and trismus (lock jaw) and photo(b) shows tonic or board like rigidity and Opisthotonus

Case 5

If a child is unimmunized, or immunization is incomplete for tetanus, a dose of the appropriate vaccine for age should be given, along with tetanus immune globulin (TIG) if the wound is considered dirty. As this child is 5 years old, DTaP would be the best choice according to the childhood immunization schedule.

Case 6

- Intramuscular immune serum globulin can prevent measles if given within 6 days of exposure
- Live vaccination is given 3 months later

Case 7

- a. Rubella
- b. Measures for her mum include: test immediately for Rubella antibodies
 - Negative and remain negative means she escaped infection
 - Positive for Rubella Ab IgG means she is immune
 - Negative and turn up positive means she got the infection(If the mother got the infection; abortion is much better than IVIG)

Case 8

- a. Important 4 investigations include:
 - Viral markers to exclude other causes of hepatitis ; HBV,HAV,HCV,CMV
 - Heterophile antibody tests to confirm infectious mononucleosis
 - Sepsis screen :Blood culture, throat swab
 - Prothrombin time assesses severity of hepatitis
- b. Diagnosis: Infectious mononucleosis with EBV hepatitis

Case 9

- a. Erythema infectiosum
- b. Parvo B19 virus

Case 10

- a. Varicella
- b. Varicella associated cerebellitis and cerebellar ataxia
- c. Clinical recovery is typically rapid, occurring within 24-72 hr, and is usually complete without treatment

Case 11

- a. Hand Foot and Mouth disease
- b. Coxsackie A virus

Case 12

- a. Mumps complicated with meningoencephalitis and orchitis
- b. CT scan brain and ,when hemodynamically stabilized, lumbar puncture
- c. Lumbar puncture likely shows evidence of viral meningitis
 - Increased pressure of cerebrospinal fluid
 - Increased protein
 - Normal sugar
 - Dominance of lymphocytes in the cell population
 - No bacteria

Case 13

- a. Mumps complicated with acute pancreatitis and viral myocarditis
- b. Investigations are
 - For myocarditis : chest x ray (cardiomegaly), ECG, and Echocardiography
 - For acute pancreatitis: serum lipase, serum calcium, lipid profile, abdominal ultrasound and CT

Neonatology

Question 1

- A. Chest compressions should not be started. Positive-pressure ventilation should continue
- B. You should stop chest compressions. You should continue positive-pressure ventilation
- C. If the baby's heart rate remains below 60 beats per minute, you should give epinephrine while continuing chest compressions and ventilation
- D. In the absence of shock or a history of acute blood loss, routine administration of a volume expander is not recommended
- E. Your team should insert an umbilical venous catheter or an intraosseous needle. During cardiopulmonary collapse, a peripheral intravenous catheter is unlikely to be successful and attempts at insertion may delay appropriate therapy

Question 2

- A. You can increase the room temperature, prepare a thermal mattress, prepare a polyethylene plastic bag or wrap, and pre-warm a transport incubator if the baby will be moved after birth
- B. You should decrease the oxygen concentration
- C. You should start positive-pressure ventilation

Case 3

- a. Fluoroscopy of the chest
- b. Phrenic nerve palsy associated with Erb's palsy

Case 4

Fracture of right clavicle

Case 5

- a. Adrenal hemorrhage (difficult breech delivery ,and possible asphyxia at birth are risk factors in addition to bleeding tendency with prolonged PT,PTT)
- b. Emergency abdominal ultrasonography
- c. Initial 4 lines of treatment after securing ABC:
 - Fresh blood transfusion and follow up of hemoglobin
 - Fresh plasma transfusion and follow up of PT and PTT
 - Vitamin k therapy
 - Phototherapy and follow up of TSB

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Case 6

- a. Neonatal sepsis suggested by:
 1. Risk factors: Premature Rupture of membranes 21 hours, Maternal intrapartum fever 38.1C
 2. Not doing well neonate pale and mottled respiratory distress and lethargy
- b. Chest x ray shows nonspecific coarse opacities of both lung fields more on the right (in the course of sepsis ;neonatal pneumonia is suggested)
- c. Sepsis screen (discuss) ,blood glucose , electrolytes and blood gases

Case 7

- a. There is Pneumatosis-intestinalis and thickened intestinal wall
- b. NEC
- c. Hold enteral feeds, NGT, start TPN→ obtain sepsis workup → empiric antibiotics→ surgical consult (see treatment for NEC)

Case 8

- a. Congenital rubella syndrome
- b. Blueberry muffin rash (see CRS): this rash is not pathognomonic to CRS ;it can be seen in congenital CMV infection and severe hemolytic disease of newborn

Case 9

- a. Physiologic jaundice exaggerated with the cephalhematoma
- b. Only phototherapy is required

Case 10

- a. ABO incompatibility
- b. Investigations
 - Reticulocytic count (RC)
 - Direct coombs test
 - Blood film
 - Serial assessment of Hb% ,TSB and RC

Case 11

- a. Breast milk jaundice
- b. Hold breast milk for 24-48 hours and feed formula milk(*now optional*)
(N.B: If there is no response and TSB continues to rise ,Criggler Najjar syndrome should be considered and a therapeutic trial with oral phenobarbitone should be instituted)

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Case 12**a. Diagnosis**

- Acute bilirubin encephalopathy(kernicterus)
- Secondary to hemolytic disease of newborn due to ABO incompatibility
- Risk is increased by the cephalhematoma

b. Investigations

- Direct Coombs test
- Serial follow up of TSB and Hb%
- For the cephalhematoma:
 - Skull CT
 - Brain ultrasound(To rule out intracranial hemorrhage as a cause of seizures)
- Sepsis workup (to rule out sepsis as a cause of not doing well newborn)

c. Management

- Immediate exchange transfusion
- Extensive phototherapy during waiting for and after exchange
- Serial follow up of TSB and Hb%
- IVIG

Case 13

- The most likely diagnosis is hemorrhagic disease of newborn due to vitamin K deficiency
- The 3 most important lines of treatment
 - Parenteral vitamin K
 - Fresh plasma transfusion
 - Fresh blood transfusion

Case 14

- Swallowed maternal blood
- Apt test for the bloody stool

Case 15

- Severe perinatal asphyxia
- Clinical (via Sarnat grading), Neuro imaging and EEG

Case 16

- Respiratory distress syndrome
- The 3 appropriate actions
 - Intubate, ventilate and give surfactant
 - Request chest x ray
 - Give antibiotics after sepsis workup
- Severe RDS , white lungs

Case 17

- a. Obtain a chest film and obtain an echocardiogram
- b. PDA, pneumothorax and endotracheal tube obstruction if intubated

Case 18

- a. Transient tachypnea of newborn
- b. The 3 important actions:
 - Provide supplemental oxygen as needed
 - Request sepsis workup (blood and chest x ray)
 - Initiate empiric antibiotics combinations till cultures come back negative

Case 19

See your text book

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