

Pediatrics II

New - 2018

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Infectious diseases

Childhood exanthemas

Measles

Rubella

Scarlet fever

Roseola infantem

Erythema infectiosum

Varicella zoster

**Exanthema = rash +
fever**

**Enanthem = mucous
membrane eruption +
fever**

It's a clinical diagnosis and include many causes, such as: infections, drugs ..
etc

To reach a diagnosis in the exanthemas, there are 3 golden questions to
ask:

- 1) Exposure: has the child had any sick contacts (with the same manifestations especially) consider incubation period, the onset of symptoms and the prodromal period.
- 2) Vaccination: has the child been vaccinated against the organism.
- 3) Past history: has the child had this before? (you can't have measles twice)

**Prodrome : period
between
appearance of
symptoms and rash**

** Clinically they are very similar: URT sx: runny nose, sore throat, sneezing

1) Measles (rubeola , sarapion)

- The causative agent is an RNA virus of only one serotype
- Also known as 10 – day measles
- Spread via respiratory droplets
- Highly contagious , infective 5 days before and 5 days after the lesion appear
- Peak age is 5-10 years
- Incubation period : 10-12 days
- Clinical features :
 - 3Cs : cough , coryza , conjunctivitis (eyes very congested mom will notice)
 - Fever for several days which is moderate to high and lasts for 6-7 days.
 - +/- photophobia
 - kopliks spots : enanthen which is pathognomonic for measles (make sure it's not milk !) , usually disappear after 24 h , found opposite to the 3rd molar (near stenson duct)
 - rash : dark (violet) , may coalesce, macular starts at head (nape of neck and behind ears) and spreads downward , fades in same manner.(face -1st days ,trunk -2nd day, lower limbs – 3rd day)
 - petechiae : not worrisome UNLESS they become big (ecchymotic) which signifies a bad prognosis and that the child is malnourished.
 - generalized LAP .
- Diagnosis: mainly clinical.
- Complications :
 - Otitis media (most common)
 - Pneumonia
 - Encephalitis / meningitis

NOTE : measles doesn't occur in 1st 6 months protected by antibodies from mother (unless mom didn't have measles vaccination before , which is unlikely

Laryngitis/ bronchitis

Less common: SSPE, occurs in 1/100.000 , symptoms :
psychological myoclonus , altered level of consciousness ,
coma and may be death.

- Treatment : supportive , vitamin A
- Prevention : immunization, Post exposure prophylaxis :

Age	management
0-6 months	Ig if mother is not immune
6-12 mo	Ig + vaccine , at separate sites
>12 mo	Vaccine only w/in 72 hours of exposure
Pregnant or immunocompromised	Ig

2) Rubella (الحصبة الألمانية)

- RNA virus, humans are the only hosts.
- Also known as 3- day measles.
- Transmission respiratory droplets, transplacental.
- Incubation period 14-21 days.
- Age : not in 1st 6 months
- Contagious 2 days before rash and 5-7 days after rash.
- Clinical features:
 - milder symptoms than measles , conjunctival congestion is mild
 - rash similar to measles, pink , begins on face and spread to rest of body , lasts approximately 3 days ; concurrent with fever (less diffuse than measles and mainly involve the face and trunk , desquamation is minimal)
 - *no staining

- retroauricular , posterior, and occipital lymphadenitis are hallmarks.
- forschiemer spots – affect the soft palate and may appear before onset of the rash.
- Complications :
 - Arthralgia in older patient.
 - Congenital rubella syndrome (infection in 1st trimester
- Diagnosis : mainly clinical
- Prevention : immunization with MMR vaccine

3) Varicella zoster (جدرى الماء)

- Chicken pox : unvaccinated child with asynchronous rash
- Shingles: elderly with unilateral vesicular rash that follows a dermatome.
- The causative agent is the VZV , a DNA herpetic virus
- Incubation: 10-21 days.
- Transmitted through respiratory secretions.
- Remains latent in sensory ganglia after recovery → reactivation in immunocompromised (shingles)
- Clinical features :
 - Prodrome of fever , malaise , anorexia , headache 24 -48 h before rash and persist for 2-4 days after rash
 - Rash : pruritic , **in various stages**
Macules -> papules -> vesicles -> crust
 - Lesions can turn hemorrhagic.
 - Crops of lesions at same time.
 - Rash begins on his trunk and spread to the extrimities
- Usually if no new lesions with everything crusted -> not contagious, so it's contagious from 24-48 h before rash and until vesicles crusted.

- Diagnosis : Tzank preparation (not necessary)
- Treatment : supportive in immunocompetent ; treat secondary infection
Consider acyclovir and VZIG in immunocompromised or those at risk for severe disease
- Complications : worse in adolescence (scarring) :
 - Varicella pneumonia seen in 15-20 %
 - Other sequels include : gullian –barre syndrome , encephalitis , cerebellar ataxia, post herpetic neuralgia and Ramsy- Hunt syndrome
 - Congenital varicella
- Prevention: second vaccine dose recommended
- Post exposure vaccine to susceptible immunocompetent ASAP and VZIG to all immunocompromised , susceptible pregnant women , and children age < 12 mo
- VZIG also for newborn whose mother had the onset of chicken pox within 5 days before delivery to 48 hours after delivery, and certain hospitalized infants.

4) Erythema infectiosum(5th disease)

- Caused by parvovirus b 19 , a DNA virus
 - Transmission : respiratory droplets
 - Incubation period : 4-28 days
 - Clinical features :
 - Prodromal of Fever , headache
 - **Rash starts on the face , flushing “slapped cheek”
 - **Erythematous diffuse macules or papules that spread on trunk and extremities, palms and soles are spared
 - **Confluence and central clearing causing net-like (reticular pattern)
- Last longer with bathing or exercise and may recur.

5th disease

- ✓ Rubeola
- ✓ Roseola
- ✓ Rubella
- ✓ Scarlet fever
- ✓ R-19

**Rash may last up to 40 days.

- Arthritis
- Infective until onset of rash
- Diagnosis : clinical
- Complications :
 - aplastic crisis in patients with hemolytic anemia
 - Hydrops fetalis in neonates during maternal infection in first trimester

5) Roseola infantum

- Caused by HH6 ,HH7.
- Almost exclusively during infancy , peak in children < 5 years , usually 6-15 months
- Incubation period : 5-15 days
- Clinical features :
 - Prolonged prodrome , may have a high fever that drops with rash , may have bulging of tympanic membrane (but NOT OM), may have bulging of anterior frontanelle (but NOT meningitis)
 - Rash : rose colored begins as papules
When fever resolves (day 3-4) maculopapular
Rash appears on trunk, arms, face, and neck
- You don't need to isolate the child
- Diagnosis : clinical
- Complications :
 - Encephalitis
 - Hemophagocytosis syndrome
 - Febrile seizures
- Treatment :supportive

6) Scarlet fever

- Caused by pyogenic toxins of group A strep.
- Infectivity during active infection diminish after weeks
- Clinical features :
 - Sudden rise of temperature associated with URTI symptoms (sore throat)
 - Rash: starts on face (forehead, cheek) typically sparing area around the mouth (circumoral pallor).

Then spreads to trunk, clavicles, axilla, arms

Fine maculopapular rash (feels like sand paper, especially in antecubital and inguinal areas)
Pastia lines.

- Enanthem: Exudative pharyngitis , strawberry tongue.
- Complications :
 - Purulent: OM, sinusitis, peritonsillar / retropharyngeal abscess.
 - Non suppurative: rheumatic fever, acute GN.

NOTE: although strep is abundant, scarlet fever is not seen a lot because not all species of strep produce erythrogenic toxin.

THE END
WRITTEN BY : Deema Al-Souri

Respiratory infections

Can be divided anatomically into infections above the sternal angle, and those below it>>>

URTI

- 1) Pharyngitis
- 2) ENT
 - a- Peritonsillar abscess
 - b- Sinusitis
 - c- Otitis
 - d- Epiglottitis
 - e- Mastoiditis
- 3) Croup
- 4) Bacterial tracheitis

LRTI

- 1) Acute bronchitis
- 2) Bronchiolitis
- 3) Pneumonia
- 4) Pleural effusion / emphysema
- 5) Tuberculosis

Other classification

Deep neck infections

- 1- Retropharyngeal abscess
- 2- Parapharyngeal abscess
- 3- Peritonsillar abscess
- 4- Ludwig angina

Fever + Stridor

- 1- Croup
- 2- Bacterial tracheitis
- 3- Epiglottitis

URTI: upper respiratory tract infections, **LRTI:** lower respiratory tract infections

Croup: Laryngo-Tracheo-Bronchitis

Ludwig's angina: serious, potentially life threatening cellulitis, or connective tissue infection, of the floor of the mouth, usually occurring in adults with concomitant dental infections and if left untreated, may obstruct the airway, necessitating tracheotomy

LRTI

- LRTI typically begins with organism acquisition via inhalation of infected droplets or contact with a contaminated surface.
- Depending on the organism, spread to distal airways occurs over varying intervals, (Bacterial infections typically progress over a few days, whereas viral infections develop gradually).
- With infection progression, an inflammatory cascade ensues with airway affected by hormone and cellular materials >> V/Q affected >> respiratory symptoms.
- Again, LRTI include: bronchiolitis, pneumonia, acute bronchitis, TB and pleural effusion.

(1) Bronchiolitis

** Inflammation of the terminal bronchioles (smallest airway).

Etiology:

RSV, most common cause (50% of cases)

Parainfluenza, adenovirus, mycoplasma, rhinovirus

Typical age:

Almost all children <2 years of age, but it's most severe in 1-2 months old.

Risk factors for severe disease: age < 12 week, prematurity, chronic pulmonary/cardiac disease, neurological disease and immunocompromised.

Pathogenesis:

Viruses infect terminal bronchiole's epithelial cells>> inflammatory obstruction/ edema, mucus and cellular debris>> ball-valve obstruction>> air-trapping and over-inflation.

Ball-valve obstruction: partial obstruction, air can enter but can't leave, gets trapped>> COPD, asthma, bronchiolitis

- Clinical presentation:**
- Mild URI prodrome
 - Decrease appetite, fever, irritability
 - Paroxysmal wheeze cough
 - Dyspnea, tachypnea
 - Apnea may be more prominent early in young infants

Wheezing has a huge Ddx, but a previously healthy infant with sudden fever and wheezing, think>>> bronchiolitis
 High fever>> adenovirus
 Low fever>> RSV

Examination:

- Wheezing, increase work of breathing, fine crackles, prolonged expiratory phase.
- Last around 12 days (worst in 2-3 days)

Differential diagnosis:

- Asthma (recurrent wheezing)
- Bacterial pneumonia
- Foreign body aspiration

Complications

Pneumonia, bacterial super-infection, dehydration, respiratory insufficiency and failure

Diagnosis:

- Clinical
- Chest X-ray: hyper-inflation with patchy atelectasis (may look like early pneumonia)
- Immunofluorescence of nasopharyngeal swab helpful>> usually RSV is isolated.

Treatment

- Usually self-limited>> supportive care
- Hospitalize if respiratory distress (ex. Respiratory acidosis)
- Trial of beta-2 agonist nebulizer (albuterol or epinephrine)
- Infant with wheezing caused by bronchiolitis do not always respond to beta- agonist
- May need mechanical ventilation
- Ribavirin may prevent need for ventilation in sever cases.
- No steroid

Prevention

In high risk patients only>> hyper immune RSV IVIG or monoclonal antibody to RSV F protein (palivizumab)

Summary: 4 months old baby, present on cold winter night, with worsening respiratory distress, decreased oral intake, was doing well until yesterday when he developed URI symptoms and low grade fever. P/E reveals wheezes throughout the chest.
Dx most likely>> RSV bronchiolitis

(2) Pleural effusion

- Fluid accumulation in the pleural space may be associated with chest pain or dyspnea.
- Transudate or exudate depending on fluid analysis>> protein and LDH.
- Many cause:
 - CHF
 - Infectious (mycoplasma)
 - Malignant (lymphoma)

(3) Empyema

- Purulent infection in the pleural space
- Chest pain, dyspnea, fever
- Usually seen with bacterial pneumonia or abscess.

(4) Tuberculosis

- An important subset of LRTI.
- Usually caused by mycoplasma tuberculosis.
- Tb is a disease, latent infection is not Tb.

A. Mycoplasma tuberculosis complex

M. tuberculosis>>>>Most common, and
M. bovis spreads from person to
M. africanum person through droplets
M. microti containing tubercle
M. canetti bacilli.

All these 5 mycoplasma complex can cause tuberculosis disease

B. Non tuberculous mycobacteria

The rest of the mycobacteria do not cause tuberculosis disease, but do cause pulmonary disease resembling Tb, but it's not transmitted person to person

Note

When a person with pulmonary or laryngeal Tb coughs, sneezes, speaks, sings, the droplets can spread and may remain suspended in the air for long periods of time, so the best way to stop transmission>> isolation of patient until treated.

High risk person:

- Low socioeconomic status
- HIV
- Elderly
- Recent immigrants

Ghon's complex: is a lesion seen in the lung that is caused by tuberculosis. The lesion consists of a calcified focus of infection and an associated lymph node.

1. Primary complex>> Ghon's complex

- Affect the lung with local infection and hilar adenopathy.
- Asymptomatic, and usually heals asymptotically.
- May be cured, or remain latent.

2. Latent infection

Reactive Tb skin test and absence of clinical or radiological findings.

3. Reactivation

- Rare (especially if acquired <2 years)
- Usually any reactivation of Tb is during teenage years.
- Risk factors for latent infection reactivation:
 - HIV, strongest risk factors>> 100X risk
 - DM
 - ESRD
 - IV drug abuse
 - Immunosuppression
 - Recent infection with M. tuberculosis

Remember

Tb is mostly pulmonary, but can also be extra-pulmonary.

Clinical picture

- As motioned, primary Tb usually asymptomatic in children, because a healthy host will wall of the organism.
- Infants more likely to have signs and symptoms.
- Occasionally>> low grade fever, mild cough, malaise, flu-like symptoms that resolve in one week.

Primary pulmonary disease

- Localized, non specific infiltrate
- Large adenopathy compared to infiltrate.
- Compression>> atelectasis and hyper-inflation
- Most completely resolve

Reactivation

- Rare without risk factors
- Fever, anorexia, weight loss, night sweats, prodrome cough, hemoptysis, chest pain.

Extra-pulmonary

Erosion into blood or lymph>> military disseminated Tb

Lungs

Military disease is either:

- Progression of primary
or
- Reactivation of latent

Body

- Spleen
- Liver
- Bone and joints (Pott's disease)
- Tb meningitis (mostly affect brainstem>> CN 3,6,7 palsies, complications: hydrocephalus)

Pott's disease: destruction of vertebral bodies leading to kyphosis.

Diagnosis

- Skin testing
 - Delayed hypersensitivity- mantoux PPD test
 - +ve 4-8 weeks after inhalation
- Positive reactions (5,10,15 mm) depend on risk factors
- <5 mm is a negative reaction

Mantoux test reaction After 48-72 hours of SQ injection	>5 mm positive in: Exposed to TB confirmed Immunocompromised Abnormal chest x-ray	False positive: Previous vaccination with BCG	False negative: - Immunocompromised - Malnourished - Patient who received live virus vaccine
	>10 mm positive in: High risk population		
	>15 mm positive in: Low risk population		

- **Best diagnosis**>> sputum from cough

Otherwise>> 3 consecutive early A.M gastric aspirates (even with PCR, still only 50% yield)

- A negative culture never exclude diagnosis
- Other sources of acid fast bacilli for stain and culture (other than sputum and gastric aspirates) are: CSF, bronchial washes, biopsy (by bronchoscopy), empyema fluid analysis, pleural biopsy.

So, a healthy person with a 5 mm induration after PPD injection is considered negative, while a child with confirmed exposure is considered positive

Note

NAAT (nucleic acid amplification)

If acid fast bacilli is +ve and NAAT is +ve>> PPV is 95%>> start treatment.

Treatment:

1. Latent TB

- INH X 9 months

-

2. Primary pulmonary TB

- INH + Rifampin X 6 months
- + Pyrazinamide in 1st 2-4 months

3. Multi drug resistant

- Add Streptomycin, Ethambutol or Ethionamide.

Unless latent TB, give at least two drugs.

INH & Rifampin:

- Bactericidal
- Good CSF level

Pyrazinamide & Ethambutol

- Bacteriostatic

Corticosteroid>> sometimes

1. Military disease
2. Pericardial/ pleural effusion

Extra-pulmonary>> treat for 10 months.

Hit hard in 1st 2 weeks of treatment
90% of bacterial load is killed in this period

Perinatal TB

If mom has positive PPD>> get chest x-ray>> if negative and she is clinically stable:

- No separation
- No evaluation of baby
- INH prophylaxis 9 months

If mom has suspected Tb at delivery:

- Separate baby until chest x-ray returns
- If chest x-ray positive>> separate until sputum culture returns
- If mother has disease:

Treat infant

- INH
- No further separation

Treat mom

- Anti-Tb therapy until culture negative for 3 months

Then

PPD skin test for infant

- Negative
 - Stop INH
- Positive
 - Continue for 9-12 months

Continue separation if mom is ill enough to be hospitalized or if resistant strain is proven or suspected.

The end
Sarah Ghaith, printed by Ahmad Shafer

Pneumonia

- It is the inflammation of lung parenchyma
- **Etiology :**
- ✓ Mainly viral (most common in all age groups): RSV, Influenza, Para-influenza, Adenovirus.
- ✓ Bacterial :
 - 0-2 months : Klebsiella, E.coli, staphylococci
 - 3 months – 3 years : S.pneumonia, H.Influenza, Staphylococci
 - Atypical organisms (Clamidia and Mycoplasma) are more in school age
 - Pnumocystis carinii : Pneumonia in immunocompromised patients

- **Note:**

Lobar pneumonia → Bacterial infections → IF recurrent (2 or more episodes in a year or at least 3 episodes at any time with radiographic clearing in-between). → Think of immune-deficiency

- **Clinical features:**

- ✓ Onset is gradual, but in bacterial is sudden
- ✓ Respiratory rate is always increased
- ✓ Mostly all patients have fever and cough
- ✓ Lower lobe pneumonia may come in picture of Acute abdomen
- ✓ Upper lobe pneumonia may come in picture of Meningitis (Meningeal signs)

Respiratory rate (Normal range):

<1 year: 30-40

1-2 years: 25-35

2-5 years: 25-30

5-12 years: 20-25

>12 years: 12-20

- **On Physical examination :**

- ✓ first see if the patient is in distress or not :

Signs of distress:

- Flaring of ala of nose
- Retraction of lower chest and intercostals spaces
- Cyanosis
- abnormal Vital signs

**Clear chest does not exclude
Pneumonia**

- ✓ Then we see signs of consolidation :

- Diminished expansion
- dull percussion note
- Bronchial breathing

- **Investigations :**

- ✓ You do not have to do Chest Xray in all cases of pneumonia

- ✓ Pneumatocele → Think of staphylococci
- ✓ In viral infection → WBC count can be normal or elevated but not higher than 20.000 cells/mm³ with lymphocyte predominance
- ✓ In bacterial infection → WBC is high and higher than 20.000 cells/mm³ with shift to the left (Exception in mycoplasma, clamidia and pertussis)
- ✓ It is very difficult to confirm bacterial infection
- ✓ Sputum culture has **NO VALUE** in diagnosis of bacterial infection
- ✓ You may do blood culture or effusion aspiration to confirm the bacterial infection
- ✓ To confirm a viral infection → Get **Nasopharyngeal swab**
- ✓ In mycoplasma infection you can do IgM titers

Note:

you may see secondary bacterial infection after viral infection especially In Influenza superimposed by staphylococci

• **Treatment :**

- ✓ In school age pneumonia → give Macrolide (Azithromycin) to cover Atypical organisms.
- ✓ After the age of 12 years consider Fluroquinilones (Do not use it before that because of it side effect (Tendonpathy))
- ✓ In Pre- school age give Amoxicillin-calvulinic acid
- ✓ In hospitalized patients the mainstay is Intravenous cefuroxime ,cefotaxime or ceftriaxone
- ✓ If the clinical feature suggests Staphylococcal pneumonia (Pneumatocele or empyema) then the initial antimicrobial therapy should also include Vancomycin or clindamycin
- ✓ In neonates we treat pneumonia as a part of Neonatal sepsis treatment with Ampicillin+Gentamycin OR cefotaxime(which penetrates the CSF so it is good for sepsis) + Ampicillin

Remember that Ceftriaxone, valium and fatty acids are competitive inhibitors with bilirubin binding to albumin so increasing the risk of jaundice .

Notes:

- ✓ Ceftriaxone is not used in baby <2 months
- ✓ Clindamycin does not penetrate CSF
- ✓ Response to treatment typically within 48-72 hours
- ✓ The first sign to improve to treatment is **fever**
- ✓ If the response is delayed → think of :
 - complications
 - bacterial resistance
 - non bacterial etiology
 - bronchial obstruction

- ✓ Don't repeat CXR if patient is doing well. There is no clinical importance since CXR changes to normal 2 weeks later after improvement.
- ✓ First thing to do in non improved case is **CHEST X-ray**.

- **Indication of admission**

- ✓ < 6 months.
- ✓ Sickle cell disease.
- ✓ Multiple lobar involvements.
- ✓ Immunocompromised.
- ✓ Toxic appearance.
- ✓ Severe respiratory distress.
- ✓ Requirement for oxygen.
- ✓ Dehydration.
- ✓ Vomiting.
- ✓ No response to oral therapy.
- ✓ Non-compliant parents.

- **Prevention**

- ✓ Flu vaccine/ pneumococcal vaccine.
- ✓ No smoking.
- ✓ Pneumococcal vaccine: conjugate type (can be given early)/ polysaccharides (pneumovax, not given before the age of 2 years).

By: Mohannad Abohamad

Upper respiratory tract infections

URTI Include:

1. Croup (LaryngoTracheoBronchitis)
2. Spasmodic Croup
3. Bacterial Tracheitis
4. Acute Pharyngitis
5. ENT conditions:
 - a. Epiglottitis
 - b. OM
 - c. Sinusitis
 - d. Para pharyngeal Abscess
 - e. Peritonsillar Abscess
 - f. Mastoiditis

1. Croup

- ☒ MCC is parainfluenza- types 1,2,3; but can be caused by many other viruses: Influenza, RSV.
- ☒ **Pathophysiology:**
 - Inflammation of glottis and subglottis.
 - Recurrences decrease with increasing growth of airway.
- ☒ **C/P:**
 - Age 3 months- 5 years old
 - Most common in the winter (parainfluenza)
 - URI (rhinorrhea, congestion) for 1-3 days, then "barking cough", hoarseness, Inspiratory stridor
 - Low grade fever
 - Worse at night.
 - Gradually resolves over 1 week
- ☒ **Complications:**
 - Hypoxia only when obstruction is complete.
- ☒ **Diagnosis:**
 - Clinical.
 - X-ray of the neck is not needed (If done, may show a tapered subglottic airway - steeple sign).
- ☒ **Treatment:**
 - It is likely caused by a virus, so mainly supportive treatment.
 - The only therapies that can significantly improve symptoms are: Aerosolized epinephrine and steroids.
 - Systemic and nebulized steroids also reduce hospital admissions, length of hospital stay and hospital readmission.

2. Spasmodic Croup:

- ☒ May be caused by Viral infections, Allergic reactions to viral antigens (rather than direct infection), or psychosocial causes.
- ☒ It is an inflammation- pale, watery edema of subglottis with preservation of epithelium.
- ☒ Clinically: Ages 1-3 years, they are fine in the daytime, but for unknown causes, they develop nocturnal stridor and difficulty breathing.
- ☒ Mild to moderate coryza and hoarseness, then sudden onset like croup (but afebrile), It Improves over several hours, and typically lasts 2-3 nights, and patient is normal between attacks.
- ☒ It has no complications.
- ☒ It is diagnosed clinically (may not respond to croup treatment), and is treated with supportive care and usually resolves with time.

3. Acute Pharyngitis

- ☒ Causes: Viruses vs. group A Beta-hemolytic strep (GABHS)
- ☒ Viral: Typical winter and spring, close contact. Ages <5 and >10
- ☒ GABHS: uncommon <2-3 years of age, more common in childhood ages 5-10, but decreases again in adolescence. All year long (but more in cold months).

Viral	Scarlet fever	Streptococcus pharyngitis
*More gradual onset, with typical URI Sx, erythematous pharynx, no pus. *Pharyngoconjunctival fever (adenovirus) *Coxsackie: May present as: 1. Herpangina 2. Acute lymphonodular pharyngitis 3. Hand-foot-mouth disease	*from GABHS that produces one of 3 streptococcal pyrogenic exotoxins (A, B, C). Exposure to each confers a specific immunity only to that toxin, so one can have scarlet fever up to 3 times *Findings of Pharyngitis+ circumoral pallor *Red, finely papular erythematous rash diffusely that feels like sandpaper *Pastia's lines	*Rapid onset of severe sore throat and fever *Headache and GI Sx frequently. *Exam- red pharynx, tonsillar enlargement with yellow, blood-tinged exudate, petechiae on palate and posterior pharynx, strawberry tongue, red swollen uvula, increased and tender anterior cervical nodes.

- ☒ **Complications:**
 - Retropharyngeal and lateral pharyngeal abscess.
 - Deep nodes in the neck.
 - Extension of localized infection of oropharynx.

- ☒ **Diagnosis:**
 - First, rapid strep test: If positive – you don't need throat culture.
 - But must confirm a negative rapid test with cultures if clinical suspicion is high.
- ☒ **Treatment:**
 - Early Rx only hastens recovery by 12-24 hours- BUT it prevents acute rheumatic fever if treated within 9 days of illness.
 - Penicillin. If allergic, Erythromycin.

4. Bacterial Tracheitis

- ☒ **MCC is Staph Aureus**
 - Less commonly caused by Moraxella catarrhalis or nontypeable H Influenza, and Viruses.
- ☒ **Pathophysiology:**
 - Inflammation- mucosal swelling at cricoid cartilage (copious, thick, purulent secretions with pseudomembranes).
- ☒ **C/P:**
 - Age 3 months- 3 years old
 - Fall/ Winter
 - May occur as a sequela 5-7 days after viral croup
 - URI (rhinorrhea, congestion), then "brassy cough", HIGH fever, respiratory distress.
 - No drooling or dysphagia.
- ☒ **Complications:**
 - Airway Obstruction- may be life-threatening!
- ☒ **Dx:**
 - Clinical plus laryngoscopy.
 - CXR- LIKE CROUP, subglottic narrowing, plus ragged tracheal air column.
- ☒ **Treatment:**
 - Anti-staphylococcal antibiotics.
 - If life threatening airway obstruction: emergent intubation or tracheostomy.

5. Epiglottitis

- ☒ **Causes:** Combination of Strep pyogenes, Strep pneumonia, Staph Aureus, Mycoplasma. All are rare.
- ☒ Before vaccines, HiB was a leading cause. After vaccine, epiglottitis has become much less common.
- ☒ **Pathophysiology:**
 - Inflammation of epiglottis and supraglottis.
- ☒ **C/P:**
 - Adult or unimmunized child.
 - Dramatic onset.
 - High fever, sore throat, dyspnea, and rapidly progressing obstruction.

- Toxic-appearing, difficulty swallowing
- DROOLING
- "sniffing-position" = a preference to sit up on his or her hands .with head leaning slightly forward and tongue sticking out. This position is preferred because it allows maximum air entry into the lungs.
- Muffled vocalization.
- Inspiratory Stridor is a late finding (when obstruction is near complete).
- No cough!
- ☒ **Complications:**
 - Complete Airway Obstruction and death: so it MUST be identified!
- ☒ **Diagnosis**
 - Clinical first- do nothing to upset the child- it is dangerous.
 - Controlled visualization of cherry-red swollen epiglottitis
 - X-RAY not needed, but may show thumb sign if preformed
- ☒ **Treatment**
 - ABCs: Establish patent airway (intubate)
 - Antibiotics: cover staph, HiB, and resistant strep: Antistaph+ 3rd generation cephalosporin.

6. Mastoiditis

- ☒ Acute Mastoiditis can be a complication of Otitis Media with Effusion
- ☒ S.pneumoniae, Nontypable H.Influenza, P.aeroginasa
- ☒ Displacement of pinna- Inferiorly and anteriorly and inflammation of posterior auricular area.
- ☒ Pain on percussion of mastoid Process
- ☒ **Dx:** When suspected or diagnosed clinically, perform CT scan of temporal bone.
- ☒ **Rx:** Myringotomy and IV antibiotics. If bone destruction: Mastoidectomy and IV antibiotics.

7. Sinusitis

- ☒ Most with URI/ most are viral / self-limited. Up to 2% are complicated by bacterial sinusitis.
- ☒ **Etiology:** S.pneumonia, nontypeable H.influenza, M.catarrhalis, S.aureus in chronic cases.
- ☒ **Pathophysiology:** Fluid in sinuses during most URIs from nose blowing. Inflammation and edema may block sinus drainage and impair clearance of bacteria.
- ☒ **Clinically:** Nasal congestion, discharge, fever and cough. Rarely: headache, face pain, decreased sense of smell.
- ☒ Sinus tenderness only in adolescent and adults, exam mostly shows mild erythema and swelling of nasal mucosa and discharge.

- ☒ **Dx: clinical:**
 - Persistent URI Sx without Improvement for at least 10 days.
 - Severe respiratory symptoms with purulent discharge and temp at least 38.9 for at least 3 consecutive days.
- ☒ **Treatment:**
 - Amoxicillin
 - Alternative: Azithromycin, Efurxime axetil, cefpodoxime.

8. Para pharyngeal and Retropharyngeal abscesses

- ☒ Occurs at any age
- ☒ Source: As mentioned above, it could be a complication of pharyngitis. Also, dental Infections, parotitis, mastoiditis, cervical adenitis are causes.
- ☒ **Symptoms:** Nonspecific-fever, Irritability, decreased oral intake, cervical swelling, Trismus (lock-jaw), dysphagia, drooling, neck stiffness, torticollis, refusal to move neck, muffled voice, stridor.
- ☒ **Examination** shows bulging of posterior or lateral pharyngeal wall
- ☒ **Complications:**
 - Carotid artery erosion
 - Horner syndrome
 - Jugular vein thrombosis
- ☒ **Definitive diagnosis-** I&D, C&S- most are polymicrobial (GABHS, anaerobes, S. aureus)
- ☒ **Treatment:**
 - IV antibiotics +/- Surgical drainage
 - 3rd Generation Cephalosporin + Ampicillin/ Sulbactam or Clindamycin.
 - Surgical drainage needed If respiratory distress or failure to improve.

9. Peritonsillar abscess

- ☒ It is a bacterial invasion through the capsule of the tonsil.
- ☒ GABHS + mixed oropharyngeal anaerobes.
- ☒ Older age: 15-25 years, Typically presents as an adolescent with recurrent history of acute pharyngotonsillitis-
- ☒ **Symptoms:** Sore throat, fever, dysphagia, drooling, trismus, "Hot-Potato Voice". (Muffled vocalization).
- ☒ **Exam:** asymmetric tonsillar bulge with displacement of uvula away from affected side is diagnostic → (Hot Potato Voice).
- ☒ **Complications:** Aspiration, Airway Obstruction.

☒ Treatment:

- Antibiotics and needle aspiration
- I&D
- Tonsillectomy if recurrence or complications (rupture with aspiration).

Bushra Tabakhi

CHILDHOOD IMMUNIZATION

IMMUNIZATION

- What is Immunization?

Is the process of inducing immunity against a specific disease.

Types of immunization:

- Passive immunization
- active immunization

PASSIVE IMMUNIZATION

- Is the administration of preformed antibodies to induce transient protection against an infectious agent.

Natural passive immunity: transplacental transfer of maternal antibodies during pregnancy can provide protection for infants in the first few months.

PASSIVE IMMUNIZATION

- Indications:
 - Immune deficiency
 - Prophylactically: Post exposure prophylaxis
 - Therapeutically: when a disease already present-suppressing the effect of a toxin or the inflammatory response

PASSIVE IMMUNIZATION

- Types:
 - Intramuscular IG
 - Intravenous immunoglobulin
 - Hyperimmune globulins
 - Monoclonal antibodies

INTRAMUSCULAR IG

- It is a concentrated antibody-containing solution prepared from large pools of human plasma.
- Primarily consists of Ig G
- Indications:
 - Prophylaxis for: • Hepatitis A • Measles
 - Immunoglobulin deficiency
- Side Effects:
 - Anaphylaxis
 - Local inflammatory reaction

INTRAVENOUS IMMUNOGLOBULIN

- Prepared from adult plasma donors.
- Predominantly IgG
- Indications:
 - Prevention of serious bacterial infections in HIV and chronic B-cell leukemia.
 - immune deficiency disorders
 - treatment of Kawasaki disease
 - Immune mediated thrombocytopenia
 - prevention of infection after BM Tx
 - TSS, GBS and anemia caused by B19

INTRAVENOUS IMMUNOGLOBULIN

- Side effects:
 - Infusion rate related: fever, headache, myalgia, chills, nausea and vomiting.
 - Anaphylactoid reaction.
 - Thromboembolic disorders.
 - Aseptic meningitis.
 - Renal insufficiency.
- 

HYPERIMMUNE GLOBULINS

- Prepared from donors with high titers of antibodies to specific agents.
- Available for:
 - Hepatitis B
 - Infant botulism
 - Rabies
 - Tetanus
 - CMV
 - Varicella-zoster

MONOCLONAL ANTIBODIES

- Antibody preparations against a single antigen.
- Indications:
 - Palivizumab: prevention of severe RSV infection in certain high-risk children.
 - Ide effects: anaphylaxis and hypersensitivity reactions

ACTIVE IMMUNIZATION

- The administration of all or part of a micro-organism or a modified product of that organism (toxoid or purified antigen) to evoke an immunologic response that mimics that of the natural infection but usually presents little or no risk for the recipient.
- Vaccines: whole or parts of microorganisms administered to prevent an infectious disease.

TYPES OF VACCINES

- Live vaccines :
 - produce active immunity by causing a mild infection. A virulent organism is weakened so that it produces an antigenic response without serious consequences.
 - included: • BCG
 - Oral Polio
 - MMR
 - varicella
 - Rotavirus
 - flu

TYPES OF VACCINES

- Killed/Inactivated Vaccines :
- They are prepared from virulent organisms or pre-formed antigens inactivated by heat, phenol, formaldehyde or any other means. Vaccines included:
 - Pertussis
 - Cholera
 - Influenza
 - Injectable Polio
 - Rabies
 - Hep A

TYPES OF VACCINES

- Toxoid: a modified bacterial toxin made nontoxic but able to induce immune response against the toxin.
- toxoid: tetanus and diphtheria.

TYPES OF VACCINES

- Parts of the organism: a cellular pertussis, HPV, and Hep B
- Polysaccharide capsules: pneumococcal, meningococcal and salmonella typh
- Polysaccharide capsules conjugate to protein carriers: Hib, pneumococcal and meningococcal.

IMMUNIZATION SCHEDULE IN JORDAN

Age	vaccine
1 st contact	BCG
2 month	DaPT1 IPV1+Hib+1HepB1
3 month	DaPT2 IPV2+Hib2+HepB2+OPV
4 month	DaPT3 IPV3+Hib3+HepB3+OPV
9 month	Measles + OPV
12 month	MMR1
18 month	DPTbooster1 +OPV booster1 +MMR2

RECOMMENDED IMMUNIZATION SCHEDULE AAP AND CDC

FIGURE 1. Recommended immunization schedule for persons aged 0 through 6 years—United States, 2012 (for those who fall behind or start late, see the catch-up schedule [Figure 3])

Vaccine	Age	1 mo	2 mo	4 mo	6 mo	9 mo	12 mo	15 mo	18 mo	19–23 mo	2–3 years	4–6 years
Hepatitis B	Birth	HepB	HepB									
Rotavirus ^a			RV	RV	RV							
Diphtheria tetanus pertussis ^b		DTaP	DTaP	DTaP	DTaP							DTaP
Inactivated poliovirus ^c		IPV	IPV	IPV	IPV							IPV
Measles, mumps, rubella ^d									MMR	MMR		MMR
Varicella ^e									Varicella	Varicella		Varicella
Hepatitis A ^f										Dose 1 ^g		Dose 2 ^g

Abbreviations: DTaP, diphtheria tetanus pertussis; HepB, hepatitis B; IPV, inactivated poliovirus; MMR, measles, mumps, rubella; PCV, pneumococcal conjugate vaccine type 13; RV, rotavirus; Varicella, varicella-zoster virus vaccine. ^aSee [www.cdc.gov/rotavirus](#) for details. ^bSee [www.cdc.gov/vaccines/imz/immunization/diphtheria-tetanus-pertussis](#) for details. ^cSee [www.cdc.gov/vaccines/imz/immunization/inactivated-poliovirus](#) for details. ^dSee [www.cdc.gov/vaccines/imz/immunization/measles-mumps-rubella](#) for details. ^eSee [www.cdc.gov/vaccines/imz/immunization/varicella](#) for details. ^fSee [www.cdc.gov/vaccines/imz/immunization/hepatitis-a](#) for details. ^gMMRV and MCV4 are also available. MCV4 use: see footnote.

IMMUNIZATION GUIDELINES

- Vaccine administration:
 - Volume/ dose: all pediatric doses are 0.5 ml
 - Preferred sites:
 - less than 18 month old: anterior lateral thigh
 - Toddlers: Anterolateral thigh or deltoid
 - Adolescents and young adults: Deltoid
 - Route: IM or SC
 - Simultaneous administration

BCG(BACILLE CALMETTE GUERIN)

- live, weakened strain of mycobacterium bovis.
- R.O.A: Intradermal.
- Dose: 0.05ml<12 mo 0.1ml>12 mo.
- Site: The recommended site of injection (all age groups) is the deltoid.
- Efficacy: 0-80% for lung TB, 75-86% for Meningitis and Miliary TB.
- Duration of Immunity: 10-15yrs
- Complications : •Erythema Nodosum
 - Deep abscess and ulceration
 - Axillary and Supraclavicular lymphadenopathy
 - Koch's phenomenon
- Contraindications : • Neonates with an immuno-deficiency.
 - Neonates receiving cortico-steroids.
 - Neonates born to a mother with HIV or suspected HIV
 - Neonates with a significant fever.
 - Neonates with a generalised septic skin condition.
 - Preterm infants.

POLIO VACCINE

- They are divided into:
 - Live Attenuated Oral Polio Vaccine(OPV- Sabin) Injectable Polio Vaccine (IPV-Salk)
 - Both vaccines contain type I,II and III strains.
- Efficacy: 95-99%
- Duration of Immunity: Lifelong if boosted.



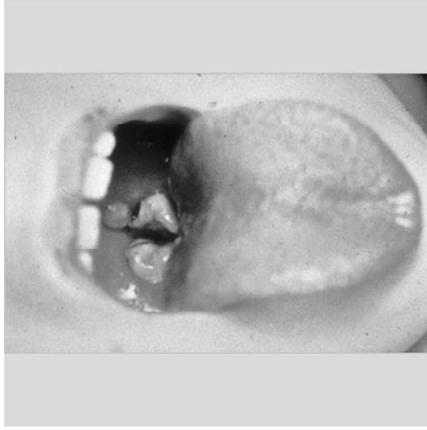
	OPV	IPV
Potency	Low (needs 4 or more doses)	High (needs 2 or 3 doses)
VAPP	1 case/2.5 million doses	None
Intestinal immunity	High (community protection)	Low (individual protection)
Secondary immunization	Yes	No
Extra injection	No	Yes
Possible combination vaccine	Unlikely	Likely
Risk of escape of wild virus	Non-existent	Possible (if produce with wild virus seeds)
Price Injection safety	Low No issue	High A risk

DPT(DIPHTHERIA, PERTUSSIS, TETANUS)

- The vaccine contains toxoid of diphtheria and tetanus with a suspension of killed whole bacillus pertussis.
- 3 doses of 0.5ml given IM at 4-8 weeks interval starting at 6 weeks. Booster given 1 yr after 3rd dose and another between 4-6 yrs of age.

DIPHTHERIA TOXOID:

- It is prepared by formaldehyde inactivation of diphtheria toxin adsorbed onto aluminum salts to increase its antigenicity. Protects against diphtheria toxin.
 - Dose: 0.5ml Site: IM
 - Efficacy: 87%
 - Duration of Immunity: 5 yrs.
 - Complications: Nil
 - Special Considerations :
Diphtheria-Tetanus(DT) is used when Pertussis vaccine is contraindicated. Td(Tetanus-Diphtheria) is used in persons 7 years of age or older



DPT(DIPHTHERIA, PERTUSSIS, TETANUS)

- Pertussis : It is used against Bordetella Pertussis.
- Dose: 0.5ml
- Site: IM
- Efficacy: 80%
- Duration of Immunity: Decreases with time
- Complications: Acute Encephalopathy (1 in 110,000) Permanent neurological sequelae(1 in 310,000)
- Contra-indications: Family history of convulsions. Family history of Sudden Infant Death syndrome Family history of adverse events following DPT administration
- Acellular vaccine less Local reaction, less Systemic, less Anaphylaxis, less Seizures, less HHE, less Temp 105F, less crying for more than 3 hrs.



TETANUS TOXOID(TT)

- It is prepared by inactivating the toxin by formaldehyde.
- TT is stable at room temperature and can survive for few weeks at 37 degrees.
- Dose: 0.5ml
- R.O.A: IM
- Efficacy: 95%
- Duration of Immunity: 5 years
- Complications : • Gullian Barre Syndrome(GBS)
 - Anaphylaxis
 - Brachial Neuritis



HEPATITIS B VACCINE

- The vaccine consists of a purified inactivated sub-unit of the Hepatitis virus. It is non-infectious.
- Dose: 0.5ml < 19yrs 1ml > 19 yrs
- R.O.A: IM
- Site: Deltoid muscle - Children and Adolescents. Anterolateral thigh – Neonates & Infants
- Efficacy: 95%
- Complications: Fever Swelling Headache Weakness
- Contraindications • Severe allergic reactions after previous dose.



HEPATITIS B VACCINE

- Special Considerations :
 - If mother is HBsAg +ve :
 - First dose: 0.5ml Hep B Ig within 12 hrs after birth & Hep B vaccine at a separate site.
 - Second dose: 1-2 months
 - Third dose: 6 months
- Infants should be tested for Anti-HBs. If +ve Vaccination effective , If -ve test for HbsAg If +ve infant is chronic carrier, If -ve Repeat tests at 0, 1 & 6months followed by anti-HBS 1 month after 3rd dose.

HEMOPHILUS INFLUENZA TYPE B(HIB)

- It is a conjugated vaccine developed against Hemophilus influenza type B bacteria.
- Given in combination with DPT at 6, 10 and 14 weeks. Booster given at 18 months.
- Dose: 0.5ml
- R.O.A: IM
- Efficacy: 95-100%
- S.E: Temporary local inflammatory reaction
- C.I: Anaphylaxis



PNEUMOCOCCAL VACCINE

- It is the current vaccine against Strep pneumoniae. Composed of capsular antigens 7,9 & 23 serotypes.
- Types: 1) Conjugated – PCV13 (Prevenar) & PCV10 (Synflorix)

2) Polysaccharide- PPSV 23

Dose: 0.5ml

R.O.A: IM or SC

Efficacy: 55-57%

C.I: Severe allergic reaction to previous dose.

Comparison between PCV and PPSV

PCV10 & 13	PPSV23
Conjugated	Polysaccharide
Immunogenic from 6 weeks -5 years of age	Immunogenic after the age of 2 years
S.E: Drowsiness Fever Loss of appetite	Muscular pain Inflammatory reaction
Herd immunity +ve	No herd immunity

MEASLES

- It is a live, attenuated vaccine prepared from multiple measles strains. It is available as: - Monovalent and in combinations (MMR , MMRV).
- Dose: 0.5ml
- R.O.A: S/C
- Efficacy:>85% at 9 months of age >90% at 12 months of age
- Duration of Immunity: Lifelong
- S.E: Mild febrile illness
- Morbiform rashes
- Encephalitis
- C.I: Immunodeficiency
- Pregnancy Neomycin Resistance



MMR(MEASLES, MUMPS, RUBELLA)

- live, attenuated , combination vaccine that protects against all three viruses.
- R.O.A: S/C
- Dose: 0.5ml Two doses are recommended, at 1 yr and 4-6yrs of age respectively. Minimum dose interval : 28 days
- Efficacy: 75-90%
- Duration of Immunity: 95% after the first dose, life long after the second.
- Complications:
 - 10% of children will develop fever, malaise & rashes 5-21 days after vaccination.
 - 3% develop joint pain lasting 18 days on average.
 - Aseptic meningitis is a rare complication.
- Contraindications :Severe Allergic reaction after previous dose, Immunodeficiency , long term immunosuppressive therapy and Pregnancy

MMR(MEASLES, MUMPS, RUBELLA)



ROTAVIRUS

- It is a live attenuated oral vaccine.
- Available as Rotarix and Rotateq
- Min age for 1st dose: 6wks-14wks & 6 days Dose Interval : 4 weeks.
- Max age for 2nd dose: 8 months
- R.O.A: Oral
- Efficacy: 61.2%
- Complications: Hypersensitivity to previous dose
- C.I: Intussusception



INFLUENZA VACCINE

- Available as a shot or nasal spray.
- Two types: -Seasonal inactivated flu vaccine - Seasonal live attenuated intra-nasal vaccine
- Min age: 6 months 2 doses in a 4 wk interval for first time vaccinators under 3 yrs of age, followed by 1 dose each year.
- Efficacy: 60%
- S.E: Local inflammatory reaction, Rhinorrhea, wheezing (for Nasal spray) Dyspnea Weakness
 - **Contraindications** : severe allergy to chicken eggs
 - severe reaction to the vaccine in the past
 - Guillain Barre Syndrome (GBS) after a prior dose of flu vaccine
 - People with moderate or severe illness

INFLUENZA VACCINE

- Who should not get vaccinated with the nasal spray? (They should get the flu shot instead.)
 - Adults 50 years of age and older or children from 6 through 23 months of age.
 - Children younger than 5 years with asthma or one or more episodes of wheezing within the past year.
 - Pregnant women.
 - People who have certain long-term health problems, muscle or nerve disorders, or a weakened immune system.
 - Anyone in close contact with someone whose immune system is so weak they require care in a protected environment.
 - Children or adolescents on long-term aspirin treatment.

MENINGOCOCCAL VACCINE

- Composed of quadrivalent A, C, W-135 and Y capsular polysaccharides.
- Given after the age of 2 years.
- Dose: 0.5ml
- R.O.A: S/C
- Duration of Immunity: 5 years
- S.E: pain , redness , swelling , Fever for 1-2 days .
- Can be given as 2 doses 3 months apart at 3 months of age in endemic areas.
- Contraindications : Sensitivity to mercury and history of GBS

VARICELLA VACCINE

- It is a live attenuated virus administered to protect against Chicken Pox caused by Varicella Zoster virus.
- 1st dose at 12-15 months and 2nd dose 4-6 years
- Dose: 0.5ml
- R.O.A: S/C
- Efficacy: 98% after 2 doses.
- S.E: Inflammatory Reaction Mild Rash
- C.I: Pregnancy Gelatin allergy High dose steroid users Chemotherapy



HEPATITIS A VACCINE

- Inactivated Hep A
- Doses: At 1 year and 2nd dose 6 months after 1st dose
- Doses are 720 ELU 1 -18 year of age • And 1440 ELU 19 years and older
- For post exposure prophylaxis. 1G(0.02ml/kg) given within 2 weeks after exposure and is effective up to 85% in preventing Hep-A up to 3 months
Available as Twinrix (Hep A+Hep B) for age 18 years and above



Vaccines Introduction:

Active vs Passive Immunity:

- **Active:** Any vaccine or toxoid or infection causes active immunity, because the body makes its own antibodies. So active immunity includes both live and killed vaccines.
This lasts longer.

- **Passive:** We give them ready antibodies. (ex. HBIG) + RSV

Synagis (palivizumab)
↳ Monoclonal Ab → binds
a protein on RSV
→ ⓪ infection

Live Attenuated	Vaccines	Notes
• Bacterial	BCG, Typhoid	
• Viral	Yellow Fever, Varicella, MMR, OPV, Rota	Live! Yellow chickens perform MMR dance, ROTating around Sabin (OPV)!

Killed Inactivated	Vaccines	Notes
• Bacterial	DTaP, Hep B, HiB, PCV, MCV	-DTP, Hep B, HiB are always given together -HiB, PCV, MCV all encapsulated polysaccharides -Hep B and DTP are protein subunits
• Viral	Hepatitis A, Rabies, Influenza, IPV	Always RIP

Vaccine Schedule:

- Use as an outline to study vaccines in that order
- For ease, I break them into five groups:
 - **Birth:** BCG
 - **2, 3, 4 months:** Almost identical group of vaccines
 - **9, 12, 18 months:** Similar vaccines
 - **"Booster Years":** When they first enter daycare and will meet new pathogens (4-6 yrs), and boosters at age (15-16 yrs).
 - **Special cases:** Prophylaxis, Certain groups of individuals, or optional.

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Vaccination Schedule IN JORDAN:

AGE	RECCOMENDED VACCINE	Optional, Special Cases
Birth - 1 month	BCG	Hep B
2 months	DaPT IPV Hep B HiB	Pneumococcal* Rota
3 months	DaPT IPV + OPV Hep B HiB	Pneumococcal Rota
4 months	DaPT OPV Hep B HiB	Pneumococcal
9 months	Measels OPV	
12 months	MMR	Varciella
18 months	DaPT MMR OPV	Varciella Hepatitis A Pneumococcal
4-6 years (Preschool)	DTaP Hep B HiB OPV MMR	
15 years (10 th grade)	Td MMR	
Any Age		Meningococcal, Gardasil (HPV)

*Pneumococcal can be given at 2,4,6 months or 2,3,4 months, then repeated at 18 months!

General Contraindications for all vaccines:

1. Don't give LIVE vaccines to immunocompromised or pregnant. (Breastfeeding is not a contraindication) (Remember: you CAN give a killed vaccine to immunocompromised)
2. Mild illness or fever alone is NOT a contraindication. It has to be moderate to severe illness.
3. Previous Severe anaphylactic shock or severe allergic reaction is always a contraindication.
4. Egg allergy is a contraindication for influenza and yellow fever vaccine
5. Egg allergy NOT a contraindication for MMR! (it is made in egg yolk, but still, not contraindicated)

Special Contraindications:

1. OPV- don't give to contacts of immunocompromised (for ex. They have a brother who is I.C) , also don't give to patients taking PREDNISONE.
2. HiB - not under 6 weeks and not for healthy child above 5 years
3. Rotavirus- not after 8 months
4. MMR- not before 1 year
5. Polysaccharide vaccines not under 2 years- immune system can't recognize. Give it conjugated to a protein.
6. Hepatitis A - give after 1 yr, CAN give it in severe liver disease and elderly

Each Vaccine, in order of Schedule:

Group 1: at birth

1. BCG

- Only intradermal (like PPD test)
- Given at birth (up to 1 month) in Jordan because Jordan is endemic for TB
- It is live attenuated M.Tb, whole living cell
- May give false-positive PPD test for those immunized.

Group 2: 2,3,4 months

2. DTP

- **Diphtheria, Tetanus, Pertussis** are all protein subunits
- Diphtheria and Tetanus always given together, usually with pertussis. Given at 2, 3, 4 months, 18 months, then a booster at 4-6 yrs.
- Td is given in 10th grade, then must be given every 10 years
- Some cases may need Td after wound injury.
- **DTP vs DTaP:**
 - Used to be given as DTP, but it caused many side effects (Fever around 30%), because Pertussis was given as a whole-cell. When they reduced pertussis to a protein subunit (aP= acellular Pertussis), side effects became much less.
 - You can still give DTP (not acellular) but less than 6 years. ~~Above the age of 6, you must give acellular pertussis (DTaP):~~
- **DT vs. dT**
 - Capital D means full dose, lowercase d is half the dose, given to adults.
 - Under 6 years, you give DT, but above the age 7 you give Td (half the dose of diphtheria protein)
 - Tetanus dose stays the same

- Because diphtheria and tetanus are protein subunits, we can conjugate them to polysaccharide vaccines (will be explained later)

Post-Exposure Tetanus Prophylaxis

Vaccination History	Clean, Minor Wounds		All other wounds	
	Td	TIG	Td	TIG
Unknown, <3 doses	Yes	No	Yes	yes
3+ doses (in last 10 years)	No	No	No	no

- **So:** Unknown/less than 3 doses give everything in all cases except Tetanus ImmunoGlobulins if clean wound, And if more than 3 doses in last 10 years nothing.
- But, if more than 3 doses, but more than 10 years they need prophylaxis.
- Also, leave tetanus wound open (but covered) to prevent bacteria from getting trapped.
- Tetanus is not contagious and doesn't cause bacteremia.

3. Polio Vaccine

- **Polio** is an enterovirus, transmitted feco-oral, enters the mouth goes to intestine but spreads by blood to target cell: **ant. Horn cells**.
- **Assymetrical** disease.
- **Polio** virus: has 3 serotypes with minimal herotypic immunity between serotypes
- It is rapidly inactivated by heat, formaldehyde, chlorine, UV light.
- Polio has two vaccines: Oral (OPV, also called Sabin) and IPV (Injectable).
- OPV is live, so you can only give to immunocompetent, IPV is killed, can be given to immunocompromised (I.C)

- **Polio virus** is in shed stool for 6 weeks and in I.C for longer. So is OPV- since it is shed in the stool you cannot give OPV to contacts of I.C because they might get polio.
- **IPV** is killed, but gives 99% immunity after 3 doses. BUT it does NOT induce high local intestinal immunity and allows for replication in the gut.
- **OPV** is very important for stopping endemic outbreaks.
- **IPV** rare reactions, OPV can cause VAPP→
- **VAPP - VACCINE ASSOCIATED PARALYTIC POLIOMYELITIS**
 - Mostly with the first dose, can happen to healthy recipients, I.C, or contacts of OPV recipients.
- Don't give OPV to patient taking prednisone or contacts of I.C

4. Hepatitis B

- Hepatitis B: under 5 years, little jaundice but high risk of chronicity.
- Hep B Vaccine usually given at 2,3,4 months and booster at 3-6 years.
- Only surface antigen is used for vaccine (HBsAg)
- Hep B: **positive immunity** is above 10 mIU/mL, anti-HBs titers
- **Lower vaccine response:** preterm infant, immunodeficiency and >40 years, male, smoking, obesity

Special case:

If baby born to a mother who is HBsAg positive: give two things:
 1-vaccine (1st dose)
 2-HBIG

*Give the vaccine and HBIG at two different sites (so they don't cancel each others effect)

*Give vaccine within 12 hrs of birth

*Finish all 3 vaccination series by 6 months, (and test at 9 months that they are immune)

5. HiB

- Hemophilus Influenza can either have a capsule or not. If it does not have a capsule it is called "non-typeable" or **NTHI**.
- If it has a capsule, then it can be "typed" and there are many types: HiA, HiB, HiC, etc. However, **type B** is the most invasive, which is why HiB is the only one clinically significant.
- Hemophilus Influenza type B
 - Remember: this is a **BACTERIA!** It doesn't cause **VIRAL** influenza
 - HiB causes **POEM (Pneumonia, OM, Epiglottitis, Meningitis)**
 - Less than 4% of population are carriers of HiB, (nasal flora) however this is a minority! (*rare* to have carriers)
 - **It is encapsulated** which gives it an advantage (invasive), body can't phagocytose polysaccharide capsule.
 - **No immunity** can be made to polysaccharide capsule under the age of 2, so vaccine must conjugated to a protein (usually diphtheria toxin)
 - The 3 encapsulated polysaccardies that must be conjugated to protein under 2 yrs are HiB, PCV (pneumococcal) and MCV (Meningococcal). But **HiB is the only one always given** (PCV and MCV for special cases)
 - Vaccine given 2,3,4 mo and booster at 4-6 yrs
 - **Rifampin** can be given as HiB **prophylaxis** but not treatment.

Ages for Hib

Less than 6 weeks: Don't give!	6 wks - 5 yrs: Give! (less meningitis especially)	>5 yrs, healthy: Don't give
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Vaccines HiB- conjugated to what:

- HbOC (diphtheria Protein)
- PRP- T (diphtheria toxoid)
- ACT- HiB (tetanus toxoid)
- PRP- OMP (outer membrane protein of meningococcus)

Group 3: 9, 12, 18 months**6. MMR**

- Measels given alone at 9 months, then MMR (measles mumps, rubella given at 1 year).
- Don't give MMR before 1 year
- Immunity is lifelong.
- About 95% efficiency, we give more than one dose because not everyone develops immunity from first dose.
- Made of egg yolk, BUT egg allergy NOT contraindication
- Live vaccine- don't give to pregnant or immunocompromised

Rubella:

- Rubella rash starts in face and does NOT cause peeling.
- **MMR** is live so don't give to pregnant, but women of childbearing age should be vaccinated to prevent congenital rubella syndrome.
- **Congenital rubella syndrome:** can ONLY be caused if pregnant women has PRIMARY INFECTION (first time) and gets infected early in the pregnancy.
- Baby affected presents with heart defects (PDA, Coarctation), microcephaly, caract, but usually they are ASYMPTOMATIC.
- MMR vaccine can cause arthralgia and arthritis because of RUBELLA in a minority (25%) of young adult females.

Mumps

- Most common complication of Mumps is aseptic meningitis
- Can uncommonly cause orchitis in POST pubertal males, but usually does NOT cause infertility because it is unilateral.

Measels

- 3 Cs, Kopliks spots, infective 4 days before and after rash.
- Measels starts in face, then trunk, then legs, can cause staining and peeling
- Highly contagious, causes viremia.

-MCV:

- For travelers to crowded places like hajj, military, college freshman
- Short lasting immunity (like 1 month)
- Meningococemia worse than Meningococcal meningitis
 - *Acute meningococemia may mimic a viral disease, but if it becomes fulminant-rapid progression: septic shock, DIC, acidosis, adrenal hmg, renal and heart failure!*
- **Rifampin is given for prophylaxis of contacts of patients infected with meningococcus**

-Hep A

- Vaccine given after 1 year of age
- Safe in liver disease

-Varicella

- Recommended 2 doses after 1 year, may have breakthrough infection but much milder, varicella is mild in kids but fatal in adults.
- Fetuses of mothers infected with varicella may develop Congenital varicella syndrome
- can give varicella post exposure prophylaxis within 72 hrs (vaccine and VZIG)

* Vaccines in the premature

- Give at chronological age & weight ≥ 2.0 Kg
- SYNAGIS to prevent RSV bronchiolitis *Bushra Tbakhi*
- ↳ annual influenza vaccine.

Group 5: Special Cases**-Rotavirus:**

- Vaccine is given **orally** (Note: oral vaccines: Rota, OPV)
- Less cases of acute gastroenteritis morbidity and mortality
- Vaccine is very effective but expensive
- Give at 2,3,4 months (optional because it is expensive)
- Don't give after 8 months.
- Immunity is most likely lifelong
- **RECENTLY** been shown to possibly cause INTUSSUSCEPTION
- *RotaVirus Vaccine, shown to increase intussusception as of Feb 2014
- <http://www.nejm.org/dol/full/10.1056/NEJMoa1311738>

-Pneumococcal vaccines:

- Pneumococcus- *s.pneumoniae* leading cause of meningitis in kids under 5. (unless neonate) and one of the leading causes of bacterial pneumonia in children younger than 5.
- Pneumococcus cause POBM: Pneumonia, OM, Bacteremia, Meningitis (VERY severe) (Similar to Hib-POEM)
- **PCV** (conjugated) and **PPSV** (Pneumococcal Polysaccharide vaccine) is not conjugated (to a protein)
- **PCV** (conjugated) is an optional vaccine, given to children less than 2 years old (they can't mount a response to the unconjugated form in that age), and is 10 or 13 valent. *Ex. Prevnar 13.*
- Schedule: at 2,4,6 months and then repeated at 18 months.
- **Pneumococcus has about 90 strains. 13 valent** means the vaccine contains 13 of the most virulent strains, and provides adequate protection!
- **PPSV is 23 valent** and is given to children over 2 years of age or to adults.
- **Pneumococcal vaccine** can be given as an option, but is required in special cases such as functional or anatomic asplenia (at risk for infection with encapsulated organisms)

Common childhood disease (Pertussis, Diphtheria & Tetanus)

Pertussis

Causative agent:

- Caused by *Bordetella pertussis* (gram -ve pleomorphic bacilli)
- Others with same picture:
 - **B. parapertussis*.
 - **B. bronchiseptica*.
 - *Adeno virus.
 - *chlamydia.
 - **B. Gengov*.
- Need very rich media composed of (glycerin/potato/blood agar)
- Different types can be differentiated by agglutination tests.

Epidemiology

- Highly contagious with attack rate >90%.
- Human is the only known host & rarely isolated from asymptomatic.
- Transmitted by droplets infection. & I.P. =6-14 days.
- Most susceptible < 5 years ((Highest mortality <1 year))
- Adults may act as reservoir for children.
- Immunity due to vaccine isn't life-long but it's life-long after true infection.

Clinical picture

The disease lasts 6-8 weeks & has the following phases:

- Catarrhal phase (Pre-paroxysmal):
 - ✓ Lasts for 1-2 weeks & highest contagious stage.
 - ✓ Characterize by: -Rhinorrhea & excessive lacrimation/ Conjunctival injection/ Mild cough & wheezes/ Mild fever.
- Pre-paroxysmal stage:
 - ✓ Last for 2-4 weeks & less contagious than catarrhal stage.
 - ✓ Characterize by: -Attacks of 5-10 forceful expiratory cough followed by sudden massive aspiratory whoop due to passage of air in narrowed glottis/ Attacks initiated by: (eating or drinking, yawning, sneezing, exercise).
- Convalescent stage:
 - ✓ Lasts for 1-2 weeks.

- ✓ Decreased cough frequency & severity but chronic cough may persist for months.

Complications

- Pneumonia due to *B. pertusis* or others.
- Atelectasis due to mucus plug.
- Pneumomediastinum
- Pneumothorax
- Sever subcutaneous emphysema.
- Bronchiectasis.
- Facial engorgement, epistaxis & subconjunctival hemorrhage, even cerebral hemorrhage.
- Hernia & even diaphragmatic rupture.
- Post-cough vomiting → Alkalosis → seizures.
- Anoxic brain damage.

Diagnosis:

- History of contact or incomplete immunization.
- WBCs increase with absolute lymphocytosis.
- X-ray - Perihilar infiltrate /Atelectasis/ Shaggyht shadow.
- Definitive diagnosis by isolation then culture or fluorescent AB stain.

Differential Diagnosis:

- Includes infection caused by other organisms that provokes an intense cough response, such as *B. parapertusis*, *C. pneumoniae*, *C. trachomatis*, *B. bronchiseptica*, and adenoviruses.
- A foreign body produces similar coughing and can be distinguished by sudden onset of symptoms and by roentgenography and endoscopy.

Treatmen:

- Erythromycin: which eliminate the m.o. within 4 days & decrease period of communicability but doesn't decrease duration of the disease.
- Supplementary: steroid/ ventoline/ O₂/ IV fluid.

Prevention:

For contact we give:

- If < 7 years - Booster dose *of* erythromycin.
- If > 7 years - Erythromycin for 10-14 days.

Diphtheria

Causative agent and Pathophysiology:

- Caused by corynebacteria Diphtheria (gram -ve Non-spore forming)
- It has 3 species (Mitis, Intermedius, Gravis)
- Two strain cause the disease; toxogenic & non-toxogenic but% of neuritis & myocarditis is more with toxogenic strain & the exotoxins produce when the bacteria infected by virus [Bacteriophage].

Epidemiology

- Increase % in winter & in crowded areas (low socioeconomic class).
- Transmitted by droplets infection. & I.P= 2-4 days.
- Human is the only reservoir & 80% of infections are in the non-immunized <15 years.

Clinical picture

- Depends on: (Spread of toxin / Immunity of the patient/Site of infection) & Divided to:
 - ✓ Pharyngeal (Tonsillar): The most common (low grade fever, Malaise, Sore throat, Bilateral cervical lymph nodes, Neuritis, Myocarditis in 10%, Membrane formation [Necrotic epithelium & inflammatory cells].
 - ✓ Nasal: Very uncommon (Usually in infants with mild course which resemble common cold).
 - ✓ Laryngeal: Due to extension from pharynx pseudomembrane. (Airway obstruction, strider or hoarseness).
 - ✓ Cutaneous: In warm climate which undistinguishable from skin infection.

Complications:

- Myocarditis in 10%- Arrhythmias & Heart failure.
- Peripheral neuropathy of Palate, Eye muscle and Extremities.

Diagnosis: Culture from membrane [Tellurite culture media], Microscopy is not reliable.

Treatment:

- Neutralize the toxin which should be given within 48hrs before toxin attach to tissue.
- Kill the bacteria [Penicillin+ Erythromycin]

- stop the antibiotic after 3 -ve subsequent cultures.
- For carriers: Benzathin penicillin+ Erythromycin.

Prevention:

Treat relatives

Prognosis: In past death due to airway obstruction from membrane (30-50%). Now death due to myocarditis (<5%).

Tetanus

Causative agent:

- Clostridium tetani (Spore bearing anaerobe)
- Produce neurotropic exotoxin & the toxin reach ant. Horn cell along the nerve or blood.
- Transmitted through contaminated wound & via umbilicus in neonate & incubation period = 2-4 days.

Clinical picture:

- Gradual onset refusal of feeding & 2 days later lock jaw starts to appear with deformity and inability to open the mouth & suck.
- Stiffness of all muscles lead to board like rigidity, opisthotonus stiff limbs, clenched fists & spasm of facial muscles (risus sardonicus).
- Convulsions (tonic-clonic) precipitated by any stimulus.
- Affection of laryngeal muscle leads to cyanosis.

Causes of death:

- Prolonged laryngeal spasm.
- Laryngeal obstruction by secretion.
- Pneumonia.

Treatment:

- General: Anticonvulsant
- Specific: Antitoxin (Anti-tetanic serum) 100,000 unit [50,000 IM & 50,000 IV]/ penicillin to prevent secondary infection & eradicate clostridia tetany.

Prevention:

- It's completely preventable by vaccination of the pregnant mother and we give three injections (1st at 1 week, 2nd at 4 weeks, 3rd at 7 month).

Gastroenteritis

- Gastroenteritis is inflammation of the lining of the stomach and small and large intestines.
- Gastroenteritis is usually uncomfortable but self-limited. Electrolyte and fluid loss is usually little more than an inconvenience to an otherwise healthy adult but can be grave for people who are very young elderly, or debilitated or who have serious concomitant illnesses.
- Improvements in water sanitation in many parts of the world and the appropriate use of oral rehydration therapy for infants with diarrhea are likely responsible for this decrease.

Etiology

Infectious gastroenteritis may be caused by viruses, bacteria, or parasites.

Viruses

The viruses most commonly implicated are

- Rotavirus
- Norovirus
- Viruses are the most common cause of gastroenteritis in the US. They infect enterocytes in the villous epithelium of the small bowel. The result is transudation of fluid and salts into the intestinal lumen; sometimes, malabsorption of carbohydrates worsens symptoms by causing osmotic diarrhea.

- Diarrhea is watery. Inflammatory diarrhea (dysentery), with fecal WBCs and RBCs or gross blood, is uncommon.
- Four categories of viruses cause most gastroenteritis: **rotavirus** and **calicivirus** (predominantly the norovirus [formerly Norwalk virus]) cause the majority of viral gastroenteritis, followed by **astrovirus** and enteric **adenovirus**.

Rotavirus is the most common cause of sporadic, severe, dehydrating diarrhea in young children

- peak incidence, 3 to 15 mo.
- Rotavirus is highly contagious; most infections occur by the fecal-oral route. Adults may be infected after close contact with an infected infant.
- The illness in adults is generally mild.
- Incubation is 1 to 3 days. In temperate climates, most infections occur in the winter.

Norovirus most commonly infects older children and adults.

- Infections occur year-round, but 80% occur from November to April.
- Norovirus is the principal cause of sporadic viral gastroenteritis in adults and of epidemic viral gastroenteritis in all age groups; large waterborne and foodborne outbreaks occur.
- Person-to-person transmission also occurs because the virus is highly contagious. This virus causes most cases of gastroenteritis epidemics on **cruise ships** and in nursing homes.
- Incubation is 24 to 48 h.

Astrovirus

- can infect people of all ages but usually infects infants and young children. Infection is most common in winter.
- Transmission is by the fecal-oral route.
- Incubation is 3 to 4 days.

Adenoviruses are the 4th most common cause of childhood viral gastroenteritis.

- Infections occur year-round, with a slight increase in summer.
- Children < 2 yr are primarily affected.
- Transmission is by the fecal-oral route.
- Incubation is 3 to 10 days.

In immunocompromised patients, additional viruses (eg, cytomegalovirus, enterovirus) can cause gastroenteritis.

Bacteria

- The bacteria most commonly implicated are
 - *Salmonella*
 - *Campylobacter*
 - *Shigella*
 - *Escherichia coli* (especially serotype O157:H7)
 - *Clostridium difficile*
- Bacterial gastroenteritis is less common than viral.
- Bacteria cause gastroenteritis by several mechanisms:
 - ❖ Certain species (eg, *Vibrio cholerae*, enterotoxigenic strains of *E. coli*) adhere to intestinal mucosa without invading and produce **enterotoxins**. These toxins impair intestinal absorption and cause secretion of electrolytes and water by stimulating adenylate cyclase, resulting in watery diarrhea. *C. difficile* produces a similar toxin
 - ❖ Some bacteria (eg, *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*) produce an **exotoxin** that is ingested in contaminated food. The exotoxin can cause gastroenteritis without bacterial infection. These toxins generally cause acute nausea, vomiting, and diarrhea within 12 h of ingestion of contaminated food. Symptoms abate within 36 h.
 - ❖ Other bacteria (eg, *Shigella*, *Salmonella*, *Campylobacter*, some *E. coli* subtypes—) **invade** the mucosa of the small bowel or colon

and cause microscopic ulceration, bleeding, exudation of protein-rich fluid, and secretion of electrolytes and water. The invasive process and its results can occur whether or not the organism produces an enterotoxin. The resulting diarrhea contains WBCs and RBCs and sometimes gross blood.

- ***Salmonella* and *Campylobacter*** are the most common bacterial causes of diarrheal illness in the US. Both infections are most frequently acquired through undercooked poultry; unpasteurized milk is also a possible source.

Campylobacter is occasionally transmitted from dogs or cats with diarrhea.

Salmonella can be transmitted by consuming undercooked eggs and by contact with reptiles, birds, or amphibians.

- Species of ***Shigella*** are the 3rd most common bacterial cause of diarrhea in the US and are usually transmitted person to person, although foodborne epidemics occur.

***Shigella dysenteriae* type 1** (not present in the US) produces Shiga toxin, which can cause hemolytic-uremic syndrome

- Several different subtypes of *E. coli* cause diarrhea.

(1) Enterohemorrhagic *E. coli* is the most clinically significant subtype in the US. It produces Shiga toxin, which causes bloody diarrhea (hemorrhagic colitis).

- *E. coli* O157:H7 is the most common strain of this subtype in the US.
- Undercooked ground beef, unpasteurized milk and juice, and contaminated water are possible sources.
- Person-to-person transmission is common in the day care setting.
- Outbreaks associated with exposure to water in recreational settings (eg, pools, lakes, water parks) have also been reported.

(2) **Enterotoxigenic *E. coli*** produces two toxins (one similar to cholera toxin) that cause watery diarrhea. This subtype is the most common cause of **traveler's diarrhea** in people visiting the developing world.

(3) **Enteropathogenic *E. coli*** causes watery diarrhea.

(4) **Enteroinvasive *E. coli*** causes bloody or nonbloody diarrhea, primarily in the developing world. It is rare in the US.

➤ ***C. difficile* infection**

➤ ***Yersinia enterocolitica*** can cause gastroenteritis or a syndrome that mimics appendicitis.

it is transmitted by undercooked pork, unpasteurized milk, or contaminated water.

➤ Several ***Vibrio*** species (eg, *V. parahaemolyticus*—see page [Noncholera Vibrio Infections](#)) cause diarrhea after ingestion of undercooked seafood. *V. cholerae* sometimes causes severe dehydrating diarrhea in the developing world and is a particular concern after natural disasters or in refugee camps.

➤ ***Listeria*** causes food-borne gastroenteritis.

➤ ***Aeromonas*** is acquired from swimming in or drinking contaminated fresh or brackish water.

➤ ***Plesiomonas shigelloides*** can cause diarrhea in patients who have eaten raw shellfish or traveled to tropical regions of the developing world

Hemolytic-uremic syndrome is a serious complication that develops in 2 to 7% of cases, most commonly among the young and old

Parasites

The parasites most commonly implicated are

- *Giardia*

- *Cryptosporidium*

➤ ***Giardia intestinalis*** adhere to or invade the intestinal mucosa, causing nausea, vomiting, diarrhea, and general malaise.

The infection can become chronic and cause a malabsorption syndrome.

It is usually acquired via person-to-person transmission (often in day care centers) or from contaminated water.

- ***Cryptosporidium parvum*** causes watery diarrhea sometimes accompanied by abdominal cramps, nausea, and vomiting.

In healthy people, the illness is self-limited, lasting about 2 wk. In immunocompromised patients, illness may be severe, causing substantial electrolyte and fluid loss.

Cryptosporidium is usually acquired through contaminated water.

- ***Entamoeba histolytica*** is a common cause of subacute bloody diarrhea in the developing world but is rare in the US

Other parasites that can cause symptoms similar to those of cryptosporidiosis include *Cyclospora cayetanensis* and, in immunocompromised patients, *Cystoisospora (Isospora) belli*, and a collection of organisms referred to as microsporidia (eg, *Enterocytozoon bieneusi*, *Encephalitozoon intestinalis*). ***Entamoeba histolytica*** is a common cause of subacute bloody diarrhea in the developing world but is rare in the US.

Symptoms and Signs

Generally, onset is sudden, with:

- anorexia, nausea, vomiting, abdominal cramps, and diarrhea (with or without blood and mucus).
- Malaise, myalgias, and prostration may occur.
- The abdomen may be distended and mildly tender; in severe cases, muscle guarding may be present.
- Gas-distended intestinal loops may be palpable. Hyperactive bowel sounds (borborygmi) are present on auscultation even without diarrhea (an important differential feature from paralytic ileus, in which bowel sounds are absent or decreased).

NOTE :Persistent vomiting and diarrhea can result in intravascular fluid depletion with hypotension and tachycardia. In severe cases, shock, with vascular collapse and oliguric renal failure, occurs.

If **vomiting** is the main cause of fluid loss, metabolic alkalosis with hypochloremia can occur. If **diarrhea** is more prominent, acidosis is more likely.

Both vomiting and diarrhea can cause hypokalemia. Hyponatremia may develop, particularly if hypotonic fluids are used in replacement therapy.

In viral infections :

watery diarrhea is the most common symptom; stools rarely contain mucus or blood.

- **Rotavirus** gastroenteritis in infants and young children may last 5 to 7 days. Vomiting occurs in 90% of patients, and fever $>39^{\circ}\text{C}$ ($>102.2^{\circ}\text{F}$) occurs in about 30%.
- **Norovirus** typically causes acute onset of vomiting, abdominal cramps, and diarrhea, with symptoms lasting only 1 to 2 days. In children, vomiting is more prominent than diarrhea, whereas in adults, diarrhea usually predominates. Patients may also experience fever, headache, and myalgias.
- The hallmark of **adenovirus** gastroenteritis is diarrhea lasting 1 to 2 wk. Affected infants and children may have mild vomiting that typically starts 1 to 2 days after the onset of diarrhea. Low-grade fever occurs in about 50% of patients.
- **Astrovirus** causes a syndrome similar to mild rotavirus infection.

In Bacterial infections:

- Bacteria that cause invasive disease (eg, ***Shigella*** , ***Salmonella***) are more likely to result in fever, prostration, and bloody diarrhea.
- ***E. coli* O157:H7** infection usually begins with watery diarrhea for 1 to 2 days, followed by bloody diarrhea. Fever is absent or low grade.
- The spectrum of illness with ***C. difficile*** infection ranges from mild abdominal cramps and mucus-filled diarrhea to severe hemorrhagic colitis and shock.
- Bacteria that produce an enterotoxin (eg, ***S. aureus*** , ***B. cereus*** , ***C. perfringens***) usually cause watery diarrhea.

In Parasitic infections :

Parasitic infections typically cause subacute or chronic diarrhea. Most cause nonbloody diarrhea; an exception is *E. histolytica* , which causes amebic dysentery. Fatigue and weight loss are common when diarrhea is persistent

Diagnosis

- Clinical evaluation
- Stool testing in select cases
- *E. coli* O157:H7–induced diarrhea is notorious for appearing to be a hemorrhagic rather than an infectious process, manifesting as GI bleeding with little or no stool. Hemolytic-uremic syndrome may follow as evidenced by renal failure and hemolytic anemia
- Recent oral antibiotic use (within 3 mo) must raise suspicion for *C. difficile* infection

Stool testing

- If a rectal examination shows occult blood or if watery diarrhea persists > 48 h, **stool examination** (fecal WBCs, ova, parasites) and **culture** are indicated.
- However, for the diagnosis of giardiasis or cryptosporidiosis, stool antigen detection using an **enzyme immunoassay** has a higher sensitivity.
- Rotavirus and enteric adenovirus infections can be diagnosed using commercially available **rapid assays** that detect viral antigen in the stool, but these assays are usually done only to document an outbreak.
- Norovirus can be detected by **PCR** in reference laboratories
- All patients with grossly bloody diarrhea should be tested for *E. coli* O157:H7, as should patients with nonbloody diarrhea during a known outbreak.
- Alternatively, a rapid enzyme assay for the detection of Shiga toxin in stool can be done; a positive test indicates infection with *E. coli* O157:H7 or one of the other serotypes of enterohemorrhagic *E. coli*.

Adults with grossly bloody diarrhea should usually have sigmoidoscopy with cultures and biopsy. Appearance of the colonic mucosa may help diagnose amebic dysentery, shigellosis, and *E. coli* O157:H7 infection, although ulcerative colitis may cause similar lesions.

Patients with a history of recent antibiotic use or other risk factors for *C. difficile* infection (eg, inflammatory bowel disease, use of proton pump inhibitors) should have a stool assay for *C. difficile* toxin.

General tests

- Serum electrolytes, BUN, and creatinine should be obtained to evaluate hydration and acid-base status in patients who appear seriously ill.
- CBC is nonspecific, although eosinophilia may indicate parasitic infection.
- Renal function tests and CBC should be done about a week after the start of symptoms in patients with *E. coli* O157:H7 to detect early-onset hemolytic-uremic syndrome

Treatment

- Oral or IV rehydration
- Consideration of antidiarrheal agents if *C. difficile* or *E. coli* O157:H7 infection is not suspected
- Antibiotics only in select cases

REHYDRATION :

- **Supportive treatment** is all that is needed for most patients. Bed rest with convenient access to a toilet or bedpan is desirable. Oral glucose-electrolyte solutions, broth, or bouillon may prevent dehydration or treat mild dehydration.
- For patients with *E. coli* O157:H7 infection, rehydration with isotonic IV fluids may attenuate the severity of any renal injury should hemolytic-uremic syndrome develop.

- If the child is breastfed, breastfeeding should continue. If vomiting is protracted or if severe dehydration is prominent, IV replacement of volume and electrolytes is necessary
- When the patient can tolerate fluids without vomiting and the appetite has begun to return, food may be gradually restarted. There is no demonstrated benefit from restriction to bland food (eg, cereal, gelatin, bananas, toast).
- Some patients have temporary lactose intolerance.

Antidiarrheal agents:

- are safe for patients > 2 yr with watery diarrhea (as shown by heme-negative stool).
- However, antidiarrheals may cause deterioration of patients with *C. difficile* or *E. coli* O157:H7 infection and thus **should not** be given to any patient with recent antibiotic use or heme-positive stool, pending specific diagnosis.
- Effective antidiarrheals include loperamide or diphenoxylate.
- For children, loperamide is used.

If **vomiting** is severe and a surgical condition has been excluded, an antiemetic may be beneficial. Drugs useful in adults include prochlorperazine and promethazine . These drugs are usually avoided in children because of lack of demonstrated efficacy and the high incidence of dystonic reactions. Ondansetron is safe and effective in decreasing nausea and vomiting in children and in adults, including those with gastroenteritis.

Antimicrobials :

- Empiric antibiotics are generally not recommended except for certain cases of traveler's diarrhea or when suspicion of ***Shigella* or *Campylobacter*** infection is high (eg, contact with a known case). Otherwise, antibiotics should not be given until stool culture results are known, particularly in children, who have a higher rate of infection with *E. coli* O157:H7 (antibiotics increase the risk of hemolytic-uremic syndrome in patients infected with *E. coli* O157:H7).

- In proven bacterial gastroenteritis, antibiotics are not always required. They do not help with ***Salmonella*** and prolong the duration of shedding in the stool. Exceptions include immunocompromised patients, neonates, and patients with *Salmonella* bacteremia.
- Antibiotics are also **ineffective** against toxic gastroenteritis (eg, *S. aureus*, *B. cereus*, *C. perfringens*). Indiscriminate use of antibiotics fosters the emergence of drug-resistant organisms.
- However, certain infections do require antibiotics
- Initial management of ***C. difficile*** colitis involves stopping the causative antibiotic if possible. Mild cases are treated with oral metronidazole. More severe cases should be treated with oral vancomycin. Unfortunately, recurrences are common with either regimen, occurring in about 20% of patients. A newer drug, fidaxomicin, may have a slightly lower relapse rate but is expensive. Many centers are using fecal microbial transplantation for patients with multiple recurrences of *C. difficile* colitis. This treatment has been shown to be safe and effective
- For **cryptosporidiosis**, nitazoxanide may be helpful in immunocompetent patients.

Prevention

- Two live-attenuated oral rotavirus vaccines are available that are safe and effective against the majority of strains responsible for disease. Rotavirus immunization is part of the recommended infant vaccination schedule
- In general, proper procedures for handling and preparing food must be followed. Travelers must avoid potentially contaminated food and drink.
- To prevent recreational waterborne infections, people should not swim if they have diarrhea.
- Infants and toddlers should have frequent diaper checks and should be changed in a bathroom and not near the water.
- Swimmers should avoid swallowing water when they swim.
- Infants and other immunocompromised people are particularly predisposed to develop severe cases of salmonellosis and should not be exposed to reptiles, birds, or amphibians, which commonly carry *Salmonella*.

- Breastfeeding affords some protection to neonates and infants.
- Caregivers should wash their hands thoroughly with soap and water after changing diapers, and diaper-changing areas should be disinfected with a freshly prepared solution of 1:64 household bleach (¼ cup diluted in 1 gallon of water).
- Children with diarrhea should be excluded from child care facilities for the duration of symptoms.
- Children infected with enterohemorrhagic *E. coli* or *Shigella* should also have two negative stool cultures before readmission to the facility

Source : <http://www.merckmanuals.com/professional/gastrointestinal-disorders/gastroenteritis/overview-of-gastroenteritis>

Organized by Deema Al Souri

Necrotizing enterocolitis

It is an acquired disease, primarily of preterm or sick neonates, characterized by mucosal or even deeper intestinal necrosis. It is the most common GI emergency among neonates. Over 85% of cases of necrotizing enterocolitis (NEC) occur in premature infants.

Risk factors

- ☒ Prematurity – the most important.
- ☒ Prolonged rupture of the membranes with amnionitis.
- ☒ Birth asphyxia.
- ☒ Small-for-gestational-age infants.
- ☒ Congenital heart disease.
- ☒ Exchange transfusions.
- ☒ Three intestinal factors are usually present:
 1. A preceding ischemic insult
 2. Bacterial colonization
 3. Intraluminal substrate (ie, enteral feedings)

Etiology

The exact etiology is not clear. It is believed that an ischemic insult damages the intestinal lining, leading to increased intestinal permeability and leaving the intestine susceptible to bacterial invasion.

NEC rarely occurs before enteral feedings and is less common among breastfed infants.

The initial ischemic insult may result from vasospasm of the mesenteric arteries, which can be caused by an anoxic insult triggering the primitive diving reflex that markedly diminishes intestinal blood flow.

Intestinal ischemia may also result from low blood flow during an exchange transfusion, during sepsis, or from the use of hyperosmolar formulas. Similarly, congenital heart disease with reduced systemic blood flow or arterial O₂ desaturation may lead to intestinal hypoxia/ischemia and predispose to NEC.

NEC may occur as clusters of cases or as outbreaks in neonatal ICUs. Some clusters appear to be associated with specific organisms (eg, *Klebsiella*, *Escherichia coli*, coagulase-negative staphylococci), but often no specific pathogen is identified.

Symptoms and signs

- ☒ Feeding difficulties and bloody or bilious gastric residuals (after feedings) that may progress to bilious emesis.
- ☒ Ileus manifested by abdominal distention, or gross blood in stool.
- ☒ Sepsis may be manifested by lethargy, temperature instability, increased apneic spells, and metabolic acidosis.

Diagnosis

- ☒ Detection of blood in stool.
- ☒ Abdominal x-rays

Early x-rays may be nonspecific and reveal only ileus. However, a fixed, dilated intestinal loop that does not change on repeated x-rays indicates NEC. X-ray signs diagnostic of NEC are pneumatosis intestinalis and portal vein gas.

Pneumoperitoneum indicates bowel perforation and an urgent need for surgery.

Complications

- ☒ Necrosis begins in the mucosa and may progress to involve the full thickness of the intestinal wall, causing perforation with subsequent peritonitis and often free intra-abdominal air.
- ☒ Perforation occurs most commonly in the terminal ileum; the colon and the proximal small bowel are involved less frequently.
- ☒ Sepsis occurs in 33% of infants, and death may occur.

Treatment

Support

- ☒ Nonsurgical support is sufficient in over 75% of cases.
- ☒ Feedings must be stopped immediately if NEC is suspected, and the intestine should be decompressed with a double-lumen NGT attached to intermittent suction.
- ☒ Fluid resuscitation.
- ☒ TPN is needed for 14 to 21 days while the intestine heals.
- ☒ Broad spectrum antibiotics.
- ☒ The infant requires close monitoring; frequent complete reevaluation.

Surgery

- ☒ Surgical intervention is needed in < 25% of infants.
- ☒ Absolute indications are intestinal perforation (pneumoperitoneum), signs of peritonitis, or aspiration of purulent material from the peritoneal cavity by paracentesis.

- ☒ It should be considered for an infant with NEC whose clinical and laboratory condition worsens despite nonsurgical support.
- ☒ During surgery, gangrenous bowel is resected, and ostomies are created. With resolution of sepsis and peritonitis, intestinal continuity can be reestablished several weeks or months later.

Prevention

- ☒ At-risk infants should be fed breast milk, and feedings should begin with small amounts that are gradually increased according to standardized protocols. (Preterm formula is an appropriate substitute if breast milk is not available.)
- ☒ Hypertonic formula, drugs, or contrast material should be avoided.
- ☒ Polycythemia should be treated promptly.
- ☒ Probiotics (eg, *Bifidus infantis*, *Lactobacillus acidophilus*) help prevent NEC, but further studies to determine optimal dosing and appropriate strains are required.

Source: <http://www.msdmanuals.com/professional/pediatrics/perinatal-problems/necrotizing-enterocolitis>

Necrotizing Enterocolitis (NEC)

Pathogenesis

Necrotizing enterocolitis may be related to an **ischemic insult** that damages the bowel lining and hampers mucus production, rendering the bowel susceptible to infection. Mucosal damage and colonization lead to intramural hemorrhage, mucosal edema, necrosis, ulceration, membrane formation, gangrene, and perforation.

NEC is associated with **prematurity**, polycythemia, congenital heart disease (including Patent Ductus Arteriosus), umbilical artery catheterization, birth asphyxia, hypertonic formula, maternal cocaine use, and rapid feeding advancement.

Management

Supportive management (in NICU) addresses temperature, ventilation, circulation, electrolyte disturbances and anemia; **x-ray every 6 hours** for the first 12 to 48 hours (high perforation risk); follow CBC, Chem, ABGs; patient should be kept NPO with gastric suction and total parenteral nutrition. **To control infection**, a broad-spectrum antibiotic combination that provides gram-negative, gram-positive (including staphylococcal species), and anaerobic coverage (blood cultures) is indicated. **Surgical resection** is required in the event of perforation, failure of medical therapy, abdominal wall cellulitis (erythema, warmth, induration), localized tenderness or mass.

Breakout Points

- **NEC must** be considered in all premature infants with any abdominal symptoms
- Long-term **sequelae** of **NEC** include strictures and short bowel syndrome (SBS), which can result in severe malabsorption, depending on the amount of bowel resected
- Treatment includes bowel rest, antibiotics, and supportive care

Fever of unknown origin

FUO is defined as temperature greater than 100.4° F (38° C) lasting for >14 days without an obvious cause despite a complete history, physical examination, and routine screening laboratory evaluation.

Etiology

- ☒ Infections, rheumatologic (connective tissue or autoimmune) diseases, or autoinflammatory diseases. Infections are the most common cause of FUO in children.
- ☒ Neoplastic disorders should also be seriously considered, although most children with malignancies do not have fever alone.
- ☒ Drug fever: it is usually sustained and not associated with other symptoms. Discontinuation of the drug is associated with resolution of the fever, generally within 72 hour, although certain drugs, such as iodides, are excreted for a prolonged period with fever that can persist for as long as 1 month after drug withdrawal.
- ☒ Most fevers of unknown or unrecognized origin result from atypical presentations of common diseases.
- ☒ Factitious fever or fever produced or feigned intentionally by the patient (Munchausen syndrome) or the parent of a child (Munchausen syndrome by proxy) is an important consideration.

History

- ☒ The impact the fever has on the child's health and activity.
- ☒ Weight loss.
- ☒ The use of drugs, medications, or immunosuppressive therapy.
- ☒ History of unusual, severe, or chronic infection suggesting immunodeficiency.
- ☒ Immunizations.
- ☒ Exposure to unprocessed or raw foods; history of pica and exposure to soil-borne or waterborne organisms; exposure to industrial or hobby-related chemicals.
- ☒ Blood transfusions.
- ☒ Domestic or foreign travel.
- ☒ Exposure to animals; exposure to ticks or mosquitoes.
- ☒ Ethnic background.
- ☒ Recent surgical procedures or dental work.
- ☒ Tattooing and body piercing; sexual activity.

Physical examination

- ☒ Child's general appearance, including sweating during fever. The continuing absence of sweat in the presence of an elevated or changing body temperature suggests dehydration due to vomiting, diarrhea, or central or nephrogenic diabetes insipidus. It also should suggest anhidrotic ectodermal dysplasia, familial dysautonomia, or exposure to atropine.
- ☒ The general activity of the patient and the presence or absence of rashes.
- ☒ A careful ophthalmic examination is important. Red, weeping eyes may be a sign of connective tissue disease, particularly polyarteritis nodosa.
- ☒ The muscles and bones should be palpated carefully. Point tenderness over a bone can suggest occult osteomyelitis or bone marrow invasion from neoplastic disease.
- ☒ Rectal examination can reveal perirectal lymphadenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis, or pelvic osteomyelitis.
- ☒ The skin is thoroughly inspected for focal erythema (suggesting a site of infection) and rash (e.g. malar rash of SLE).

Screening tests

- ☒ Complete blood count with WBC and differential count, and platelet count.
- ☒ ESR, CRP, hepatic transaminase levels.
- ☒ Urinalysis, cultures of urine and blood, and chest radiograph.
- ☒ Evaluation for rheumatic disease with antinuclear antibody, rheumatoid factor, and serum complement (C3, C4, CH50).
- ☒ Throat culture, stool culture, tuberculin skin test or interferon-gamma release assay, HIV antibody, Epstein-Barr virus antibody profile, and B. henselae antibody.
- ☒ Further tests may include lumbar puncture for CSF analysis and culture; CT or MRI of the chest, abdomen, and head; radionuclide scans; and bone marrow biopsy for cytology and culture.

Management

- ☒ The ultimate treatment of FUO is tailored to the underlying diagnosis.
- ☒ Antimicrobial agents should not be used as antipyretics, and empirical trials of medication should generally be avoided.
- ☒ Antituberculous treatment in critically ill children with suspected disseminated tuberculosis.
- ☒ After a complete evaluation, antipyretics may be indicated to control fever associated with adverse symptoms.

Source: Nelson textbook and nelson essentials

Meningitis

- **Meningitis** : inflammation of the brain **meninges** (dura mater , arachnoid mater and pia mater) , and it's evident by the abnormal WBCs presence in the CSF
- **Aseptic meningitis** : non-bacterial meningitis (negative CSF culture , could be **viral** , **drug** induced) in a patient who is NOT previously treated with antibiotic (culture can come back negative in bacterial meningitis in a patient who was previously treated with antibiotic)
- **Encephalitis** : inflammation of the brain **parenchyma**
 - Encephalitis differs from meningitis in presentation
 - encephalitis → more change in mental status , behaviours
 - A patient with meningitis and brain function abnormalities is more likely to have **meningoencephalitis**
- Dx → CSF sample taken by lumbar puncture

Table 1. Typical CSF Findings in Patients With and Without Meningitis

Parameter	Normal	Bacterial Meningitis	Viral Meningitis	Fungal Meningitis	Tuberculous Meningitis
Opening pressure (mm H ₂ O)	<180	200-500	NA	>250 (<i>Cryptococcus</i> sp)	NA
WBC count (mm ³)	0-5	100-20,000 (mean 800)	5-500 (mean 80)	20-2,000 (mean 100)	5-2,000 (mean 200)
WBC differential	No predominance	>80% PMN	>50% L, <20% PMN	>50% L	>80% L
Protein (mg/dL)	15-50	100-500	30-150	40-150	>50
Glucose (mg/dL)	45-100 (2/3 of serum)	≤40 (<40% of serum)	30-70	30-70	<40
Gram stain (% +)	NA	60-90	–	–	37-87 (AFB smear)

+: positive; *-*: negative; AFB: acid-fast bacilli; CSF: cerebrospinal fluid; L: lymphocytes; NA: not applicable; PMN: polymorphonuclear cells; WBC: white blood cells. Source: References 9, 10.

- You need to know the numbers in this figure , viral and bacterial of most importantly.
- Normal WBCs count : 0-5 (mostly LYMPHOCYTES) , in neonates, less than one month , up to 25 cells is normal
- WBCs out number in CSF is called “ pleocytosis” , and “pyuria” in urine
- **Pleocytosis** → abnormally large number of lymphocytes in the cerebrospinal fluid.
- Glucose CSF to serum ratio , so at the same time you do LP, you need to measure serum glucose , normal ratio : >2/3 , in bacterial meningitis the ratio drops to 1/ 2 (CSF glucose becomes very low)
- Normal CSF protein in neonates is up to 120 , children 20-40 , and very elevated in fungal (up to 1000,2000)

Aseptic meningitis

Viral meningitis :

- **Most common** type of meningitis ,affects children in **summer** and **late spring** , viral meningitis not seen in winter. Viral is self limiting, no sequelae
- **Route of entry** : mucosal surface of **respiratory** and **GI** tract , virus replicates in the regional lymph nodes > **viremia** > seeds in **CSF**
- **90%** of viral meningitis are caused by **enteroviruses** : polio and **nonpolio** viruses (coxsackie A, coxsackie B, echoviruses and the numbered enteroviruses)
- **Enteroviruses** → picornavirus family, small RNA viruses ,single positive-strand RNA
- Coxsackie A virus (CAV); also causes Hand foot and mouth disease
- The most common causes of viral meningitis in the United States are **non-polio enteroviruses**.
- humans are the only reservoir , route of transmission is the **feco-oral route** , short incubation period from 3-6 days
- Recurrent/chronic enteroviral meningitis → think of humoral immune deficiency, specially **X linked Agammaglobulinemia**
- **Symptoms** in neonates and infants ((which is the same in meningitis in general) :
 - fever/temperature instability(hypothermia) and
 - non-specific symptoms : vomiting , diarrhoea, rash, respiratory distress ,
 - CNS manifestations can be clear or they may show irritability, lethargy, plugging fontanel , nuchal rigidity in elder children , encephalopathy , seizures , change in mental status , focal neurological findings like hemiparesis (symptoms differ and the **absence of neurological manifestations does not exclude meningitis**)
- Clinical presentation in older children - the classical presentation :
 - Fever
 - Photophobia, Headache, Neck stiffness
 - Vomiting
- **Rash** is seen in viral meningitis, and the more severe rash occurs in **meningococccemia** , typically **non-blanchable** extended petechiae, while viral rash is blanchable
- PE:
 - **Nuchal rigidity** in more than 50%
 - **Plugging fontanel** if still open can be found
- Viral specific manifestations :
 - **conjunctivitis** in enterovirus and adenovirus
 - **Pharyngitis** and **diarrhea** are more with enterovirus
 - **Herpangina** (mouth blisters) with coxsackievirus
 - **Hand foot and mouth disease** (very painful rash) with coxsackievirus
- **Diagnosis** of enteroviral meningitis : by **PCR**



- Another virus we need to know about is : **HSV (herpes simplex virus)** :
 - HSV does not usually cause meningitis ,it causes **encephalitis**
 - Is of two types :
 - **Neonatal** HSV : causes only skin-eye disease or disseminated CNS disease (encephalitis)
 - **Postneonatal** (older children) : encephalitis with altered mental status , HSV is the most common cause of encephalitis in children
 - HSV 1 > causes gingivostomatitis ,skin infections
 - HSV 2 > genital infections
 - Incubation period : 4 days
 - Diagnosis : CSF PCR
- Other viruses that can cause meningitis / encephalitis : Varicella zoster virus , Arbovirus (viruses transmitted by arthropod-ticks) , EBV, CMV, human herpes virus and influenza (almost all viruses can cause meningitis)

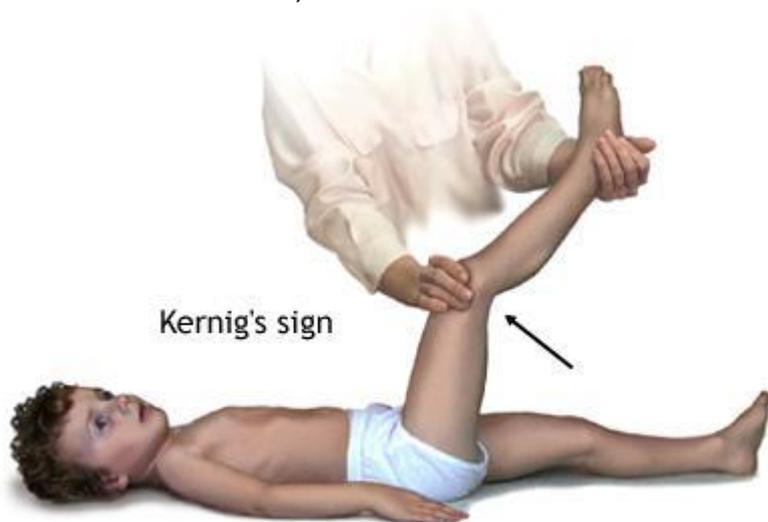
Aseptic meningitis also include non-infectious causes:

- 1) **Drug** induced meningitis : **Ibuprofen** , **bactrim** , and a common drug is **IVIg** ⇒ severe headache and photophobia after administration , treatment : just observation
- 2) **Malignancy** : recall that meningitis is defined as inflammation of the meninges evident by abnormal presence of WBCs
- 3) **Autoimmune** : Sarcoidosis , Behcet's disease , SLE
- 4) **Others** : epidermoid cyst ,heavy metal poisoning

Bacterial Meningitis

- Is a medical emergency , with a very high mortality rate , can approach 100% if not treated
- Categorized by the causing agent for each **age group**:
 - **less than 3 months** : **group B streptococcus** "GBS" is the most common (so always cover group B strep when treating less than 3 months old) , **gram negative bacilli** ⇒ both come from mother's **vaginal tract**
 - **more than 3 months** : streptococcus pneumoniae and neisseria meningitidis
 - **Adolescents** above 10 years : more Neisseria meningitidis
- **Neisseria meningitidis** :
 - comes from **nasopharynx** , affects all ages (except less than 3 months), more common with **asplenic** patients , and **complement deficiency** (recurrent Neisseria meningitidis → think of complement deficiency)
 - Petechial rash and meningitis signs, very dangerous, rapid killer , but respond well to Abx
- **Streptococcus pneumoniae** :
 - Comes from **nasopharynx**, skull fractures , **sinusitis** ,cochlear implants, and more in patients with **asplenia**
- **Coagulase negative staph** :
 - with foreign bodies like **ventriculoperitoneal shunt "VPS"**
- **H. Influenza** :

- Comes from **nasopharynx** , in unvaccinated children
- Bacterial meningitis **symptoms**: Same as viral
 - Neonates: nonspecific
 - Older children : the previously mentioned classical symptoms
 - **Petechiae and purpura** occur with any bacterial pathogens, but more characteristic of Neisseria (**meningococemia**)
- Meningeal **signs**
 - signs of **meningeal irritation** (usually not evident in less than 2 years of age , present in **80%** not in all patients (20% -ve, not very sensitive), so you always need **LP** to diagnose), Nuchal rigidity and Kernig and Brudzinski signs are frequently not present in the neonate with meningitis:
 - **Nuchal rigidity**
 - **passively**: Involuntary muscle spasm limits passive neck flexion
 - **actively**: Patient cannot flex neck to place chin on chest
 - **Kernig sign**: is positive when the thigh is bent at the hip and knee at 90 degree angles, and subsequent extension in the knee is painful (leading to resistance) and flexion of the other knee
 - **Brudzinski sign**: head flexion provokes knee flexion (to relieve meningeal irritation)



ADAM.



- Neurological findings :
 - vary from altered consciousness to coma
 - signs of **increased intracranial pressure**:
 - **headache, plugging fontanel**, cranial nerve **palsy** → most commonly of the 3rd,4th and 6th cranial nerves
 - **Papilledema** → check by **fundoscopy** , **CT scan** is sometimes needed to rule out increased intracranial pressure , because doing **LP** in a patient with increased ICP can cause **brain herniation** , give antibiotics before you send the patient to CT
 - **seizures** : up to 30% , yet it has no prognostic value , only if continues more than 72 hours or after 48 hours of admission → could be abscess or electrolyte imbalance
 - **Cushing triad**, late sign: hypertension , bradycardia ,irregular alternative respiration (cheyne stokes breathing)
 - **CT scan,MRI** indications : altered mental status , CSF shunt, papilledema ,focal neurological deficits, increased head circumference, recurrent meningitis, empyema ,infants with citrobacter(causes brain abscess)
- **Blood culture** : 50% of pts with bacterial meningitis → positive CSF culture
 - **Blood culture** does not exclude meningitis
- LP contraindications :
 - Cardiopulmonary compromised patients
 - signs of increased ICP
 - skin infection over the site of LP
- LP is done between L3 & L4 or L4 & L5
- Take 5 samples of CSF :
 - 1. For **microbiology lab: culture** (comes out positive for up to 9 hours after Abx administration,except for Neisseria which can be cleared within one

- hour) , **stain** (can be positive with a negative culture , because it depends on the presence of bacteria live or dead), **PCR**
- 2.For **chemistry** : glucose , protein , with blood glucose sample
 - 3.**Cell count, differential**: RBC , WBC
 - 4.**Cytological**: neoplasms , tumours
 - 5.Extra sample : since LP is difficult
- **Traumatic LP** → blood with CSF→ high WBCs → should be treated presumably as meningitis
 - **Partially treated meningitis** : meningitis that was thought to be throat infection and treated with one type of antibiotic → negative culture, but high WBCs in CSF → use rapid diagnostic test to detect bacterial antigens → latex test → treat for 7-10 days
 - **Gram stain** : positive in **90%** of **pneumococcal** meningitis , **80%** of **meningococcal**
 - gram +ve diplococci → strep pneumoniae
 - gram +ve coccobacilli → GBS (in neonates)
 - gram –ve diplococci → Neisseria
 - gram –ve coccobacilli → H.influenzae
 - Bacterial meningitis patient is sicker than viral , yet you can't differentiate viral from bacterial by clinical presentation, that's why we request CSF culture to rule out bacterial meningitis
 - Management of bacterial meningitis:
 - ABC
 - Do not delay
 - Use **bactericidal** agent, Drug entry to CSF
 - **Ceftriaxone** (third generation cephalosporin) IV + **Vancomycin** IV (to cover strep pneumonia) → empiric treatment
 - Duration of therapy
 - Neisseria : 5-7 days (penicillin or ceftriaxone can be used)
 - H.influenzae : 7-10 days (use Vancomycin if ceftriaxone resistant)
 - Strep pneumonia : 10-14 days
 - **Dexamethasone**: specially with H. influenza to decrease inflammation from bacterial cells destruction and toxins release after antibiotics administration → only given 1 hour before the first dose of antibiotics
 - Complete neurological examination should be performed daily, with head circumference (for hydrocephalus)
 - Response to therapy , persistent fever?→ inadequate treatment, nosocomial infection,dexamethasone cutting , brain abscess ,empyema ,or drug fever

- Repeat LP ? → with poor response ,persistent /recurrent fever
- **Mortality rate** : if treated 5% , if not treated approaches 100%
- **Prognostic factors** : **Glasgow coma scale** at time of admission , etiologic agent which is worse with **strep pneumonia**, prolonged complicated seizures ,sterilisation of CSF and nutritional status
 - Over 10% of survivors are left with long-term neurological impairment
- before discharge make **hearing evaluation** and **developmental assessment**
- other complications : SIADH secretion, subdural effusion, obstructive hydrocephalus, ataxia, deafness, cortical blindness
- **Precautions** : droplet precautions for Neisseria and H.influenzae
- **Vaccines** : strep pneumoniae and Neisseria vaccines are available but not part of the national program
- **Chemoprophylaxis** : for **Neisseria** (for all contact in the past 7 days/medical care givers who had direct exposure to the secretions) and **H.influenzae**
 - Rifampin , if not tolerable or pregnant → Ceftriaxone

Notes

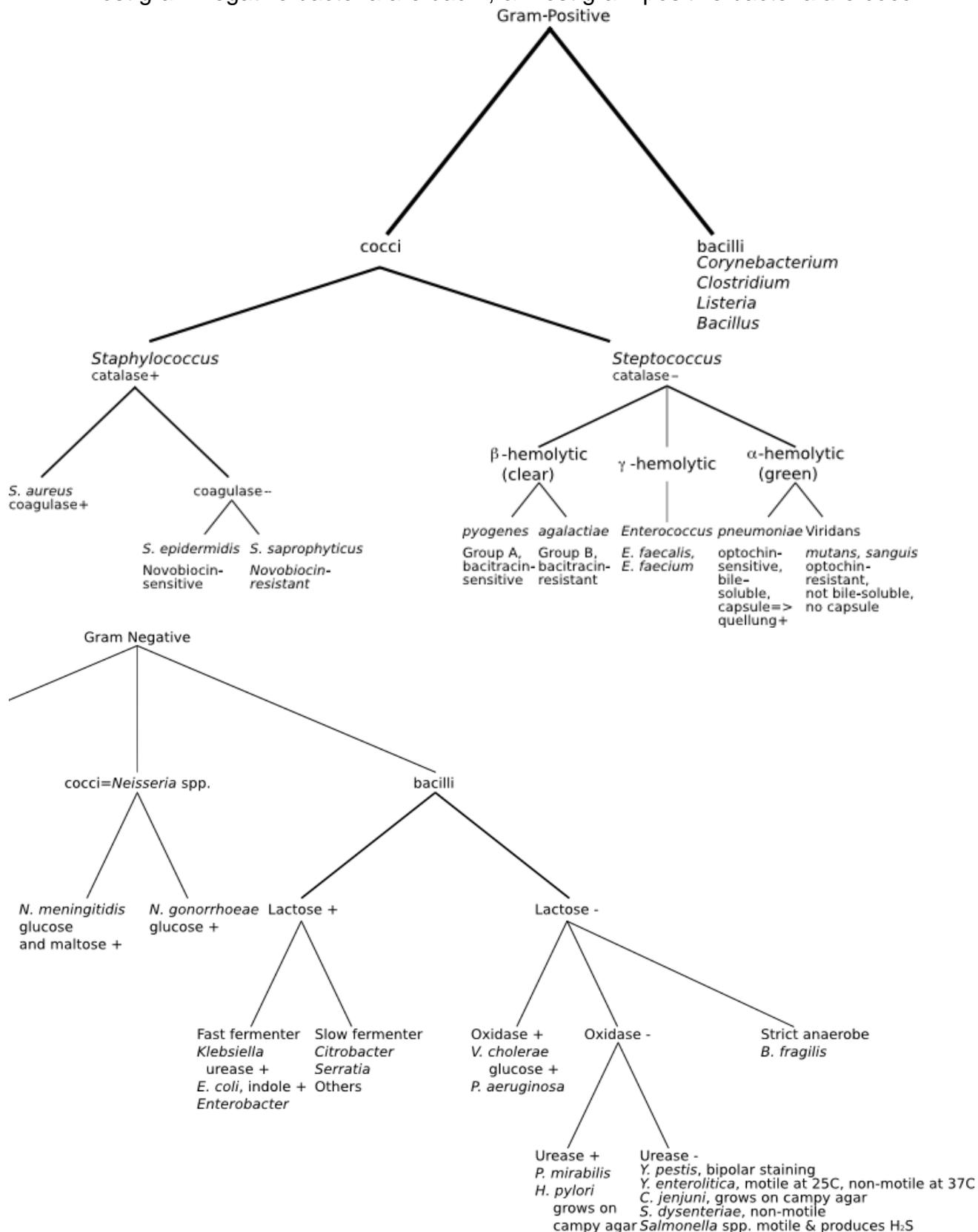
- Isolation & prophylaxis
 - S.pneumonia
 - No isolation, no prophylaxis
- N.meningitidis
 - Droplet isolation for 24 hour after Tx
 - prophylaxis → household contact + child care
 - Ceftriaxone or rifampin
 - Not given for school children

Source: Dr. Dawoud yosuf lecture
Mohammed Nawaiseh

Antibiotics in Pediatrics

Intro

- **Bacteriostatic:** Capable of inhibiting (slowing) the growth or reproduction of bacteria.
- **Bactericidal:** Capable of killing bacteria.
- most gram negative bacteria are bacilli, & most gram positive bacteria are cocci.



Hemolysis

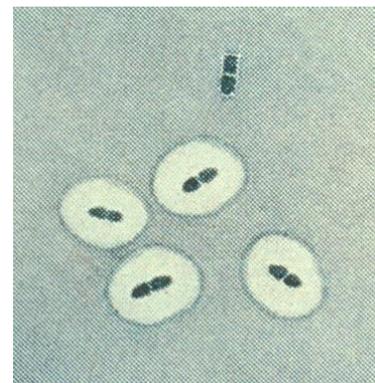
- **alpha hemolysis** → dark and greenish, hydrogen peroxide produced by the bacterium, oxidizing hemoglobin producing the green oxidized derivative **methemoglobin**.
- Beta hemolysis → complete hemolysis, area appears lightened (yellow) and transparent
- Gamma → non-hemolytic, does not induce hemolysis, the agar under and around the colony is unchanged



Hemolysis of Streptococcus spp. (left) α -hemolysis (*S. mitis*); (middle) β -hemolysis (*S. pyogenes*); (right) γ -hemolysis (= non-hemolytic, *S. salivarius*)

Quellung reaction

- antibodies bind to the bacterial capsule of **Streptococcus pneumoniae**, **Klebsiella pneumoniae**, **Neisseria meningitidis**, **Bacillus anthracis**, **Haemophilus influenzae**, **Escherichia coli**, and **Salmonella**.
- If the reaction is positive, the capsule becomes opaque and appears to enlarge.



E Coli → indole +ve

Klebsiella → urease +ve

B fragilis → Bacteroides fragilis

Lactose + : Lactose fermenters.

- SCEEK: Serratia, Citrobacter, E. Coli, Enterobacter, Klebsiella are the commonest causes of UTI

50% of UTI are extended-spectrum beta-lactamases (ESBL) → superbugs that don't respond to any Abx

S.aureus

- Types: MSSA (methicillin Sensitive S. aureus) & MRSA (methicillin Resistant S. aureus)
- Diseases:
 - Skin/Soft tissue/bone/joint infections: Cellulitis, Abscess, Osteomyelitis, Septic Arthritis
 - Central line infections: Staph. Aureus, & Staph. Epidermidis
 - Hospital acquired infections: mostly MRSA.

Streptococcus

- **S. Pneumoniae** (alpha hemolytic): Pneumonia, meningitis, otitis media, sinusitis [The most common cause of all these], bacteremia.
- **S. Pyogenes** (beta hemolytic, Group A strep, GAS): Tonsillitis, Skin/soft tissue infections (boils, abscess, cellulitis).
- **S. Agalactiae** (beta hemolytic, Group B strep, GBS): Neonatal sepsis
- **Enterococcus** (Gamma → non-hemolytic): UTI & Infective endocarditis

E coli

- UTI and Intra-abdominal infections
- Intra-abdominal infections are caused by gram negative bacteria & anaerobes

Pseudomonas

- Fever in **neutropenia, immunocompromised** patients (Opportunistic infections)
- **Hospital** acquired infections, 90% mortality, multidrug resistant

Anaerobes

- Intra-abdominal infections, **aspiration pneumonia**, brain abscess.
 - Aspiration pneumonia is common, especially in **CP** patients.
 - Brain abscesses are not common

Atypical bacteria

- **Mycoplasma, Chlamydia, Legionella**
- Pneumonia in children **>5 y** of age.

Classification

- **β-lactam antibiotics** → penicillins, cephalosporins, cephamycins, & carbapenems
- **Penicillins**
- **cephalosporins** (ceftazidime, cefepime, cefuroxime, cefotaxime, or ceftriaxone)
- **carbapenems** (meropenem, imipenem, ertapenem)
- Cephamycin → Cefoxitin, Cefotetan
- **monobactams** (aztreonam)

- Glycopeptides → **vancomycin**, teicoplanin, telavancin
- Macrolides
 - Azithromycin (azalides, does not inhibit CYP3A4)
 - Erythromycin, Clarithromycin

- Metronidazole
- **Aminoglycosides** (gentamicin, amikacin, tobramycin, kanamycin, streptomycin)
- Trimethoprim-sulfamethoxazole
- **Fluoroquinolones** →
Ciprofloxacin, Gemifloxacin, Levofloxacin, Moxifloxacin, trovafloxacin
- **Tetracyclines**
- **Anti Tb “IR PE”** → Isoniazid , Rifampicin , Pyrazinamide , Ethambutol
- **polymyxins** (polymyxin B and colistin)
- Lincosamide → clindamycin

Bactericidal	Bacteriostatic
<ul style="list-style-type: none"> • Penicillin , Cephalosporins, & all lactams • Glycopeptides • Aminoglycosides • Fluoroquinolones • Metronidazole (Flagyl) • Rifampin • Bactrim (trimethoprim- sulfamethoxazole) 	<ul style="list-style-type: none"> • Sulfonamides • Tetracyclines • Macrolides • Clindamycin • Linezolid

- **Bactericidal** agents are used for **immunocompromised** patients & for serious infections e.g. meningitis & infective endocarditis
- **Fluoroquinolones** are not used for <18 years old patients, because they affect growing cartilage and can cause tendon rupture .
 - There's no strong evidence supporting this, therefore it was recently used for complicated UTI.

β-lactam antibiotics

β-lactam antibiotics → penicillins, cephalosporins, cephamycins, & carbapenems

- **Penicillins**
 - **Natural** → PCN G , PCN V
 - **Synthetic** → nafcillin, oxacillin, cloxacillin and dicloxacillin
 - **Amino-PCN** → ampicillin , amoxicillin
 - **Ureidopenicillins** → piperacillin, carbenicillin , ticarcillin
- **cephalosporins** (ceftazidime, cefepime , cefuroxime, cefotaxime, or ceftriaxone)
- **carbapenems** (meropenem, imipenem, ertapenem)
- Cephamycin → Cefoxitin, Cefotetan
- **monobactams** (aztreonam)

Allergy to one **β-lactam** is associated with cross reaction to most (but not always all) other Latams.

Penicillin (PCN)

- Inhibit cell-wall synthesis: Bactericidal

- **5th generation** : (**ceftaroline** IV)
 - *Not used yet in children

Coverage & Usage

- **First** generation:
 - **Coverage**:
 - **Most gram-positive** cocci (Exceptions are MRSA, enterococcus).
 - **Some gram negatives** like E. coli.
 - **Anaerobic** pathogens except Bacteroides.
 - First generation cephalosporins are very similar to amoxicillin, but unlike cephalosporins, amoxicillin cannot cover MSSA.
 - **Usage**: Skin/soft tissue infections, some UTI, Group A strep infections
 - Additional: preoperative prophylaxis
- **Second** generation
 - **Coverage**: less active against gram-positive cocci than the first generation but more active against gram-negative bacilli, Haemophilus influenzae and Moraxella catarrhalis
 - **Usage**: Pneumonia & other URTI
 - Pelvic inflammatory diseases (cefoxitin: more anaerobic coverage).
- **Third** generation:
 - **Coverage**: less active against gram-positive organisms than the first generation
 - **Usage**: Meningitis, Sepsis, Pneumonia, UTI and many others
 - **Ceftazidime** has poor activity against gram-positive organisms and should be reserved for use in proven or highly suspected **P. aeruginosa**
 - **Ceftriaxone** causes the formation of "sludge" in the biliary tract and displacement of bilirubin from albumin causing **hyperbilirubinemia** (not used < 1 mo of age); Use **cefotaxime** IV instead.
- **Fourth** generation:
 - greater activity against the **gram-negative**
 - **Cefepime** is as active against Pseudomonas aeruginosa (febrile neutropenia & Hospital acquired infections)
- **Fifth** generation :
 - **Ceftaroline** has a spectrum of activity similar to ceftriaxone but with improved gram-positive activity (MRSA)
- Some organisms, including **all enterococci, Listeria, Atypical bacteria** (Legionella, Mycoplasma, Chlamydia) are ALWAYS resistant to cephalosporins

Side effects

- They're generally well tolerated.
- Oral cephalosporins may cause nausea, vomiting, & diarrhea

Carbapenems

- **Imipenem, meropenem, ertapenem, doripenem**
- Inhibit cell-wall synthesis: Bactericidal \ Very broad spectrum of activity.

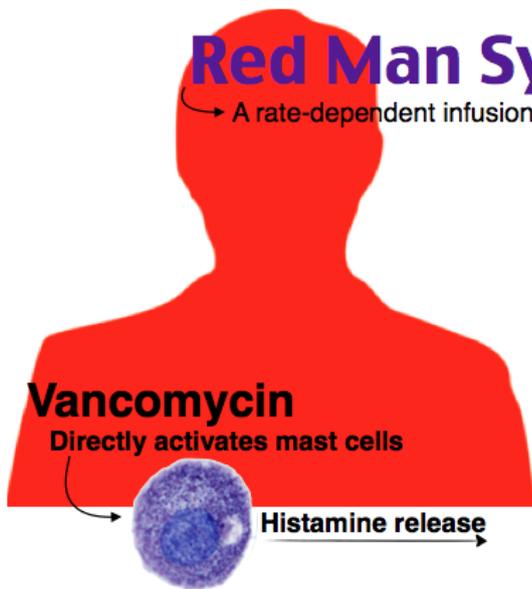
- **Cilastatin** can be combined intravenously with imipenem in order to protect it from dehydropeptidase “avoid hydrolysis” and prolong its antibacterial effect. and to reduce nephrotoxicity
- In general, tolerability to carbapenems is good.
- Stable to beta-lactamases including **extended-spectrum beta-lactamases (ESBL)**
 - It's the only drug available against ESBL
- **carbapenemase** producing **enterobacteriaceae** started to appear in some countries where carbapenems are abused leaving patients completely hopeless & in pain.
- **Carbapenems** lack the activity against *Enterococcus faecium*, **MRSA**
- **Ertapenem** lacks the activity against ***Pseudomonas aeruginosa***
- Uses:
 - Intra-abdominal infections (gram negatives & anaerobes)
 - Nosocomial pneumonia (not first line)
 - Febrile neutropenia (not first line, use Tazosyn instead)
- Side effects:
 - **Seizures** are a well-known side effect of **imipenem/cilastatin**, especially in patients who have **meningitis**.
 - Seizures occur in approximately 3% of patients who are treated with imipenem and who do not have CNS infections, but the incidence of seizures can be as high as **33%** in patients who have **bacterial meningitis**.

Glycopeptides

- **Vancomycin** IV and PO, teicoplanin IV ,telavancin
 - Teicoplanin IV is used in adults
- Inhibits bacterial cell wall synthesis; bactericidal
- Coverage & Usage
 - **Gram positive** including **MRSA** and **enterococcus**
 - Meningitis (*S. pneumoniae*)
 - Catheter-related infections (*Staph aureus*)
 - Hospital-acquired infections (*Staph aureus*)
 - Foreign body associated infections (Ventriculoperitoneal shunt “**VPS**”, prosthetic materials) (*Staph aureus* & *Staph epidermidis*)
 - *C. difficile* (PO only) ⇒ Vancomycin is used mainly IV, given PO in only one case → *C. difficile* colitis (Pseudomembranous colitis).
- Side Effects:
 - **Red man syndrome**
 - Rate dependant, Slow the infusion rate to over 2 hours and increase the dilution volume
 - Antihistamine & Steroids are given in severe cases
 - It's **not an allergic reaction**
 - **Extravasation** will cause serious injury with possible necrosis and tissue sloughing.
 - It's might cause **nephrotoxicity**

Red Man Syndrome

→ A rate-dependent infusion reaction (**not a true allergic reaction**)



Clinical

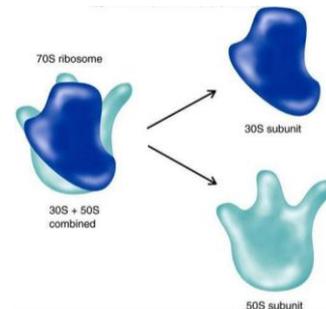
- Flushing
- Erythema
- Pruritus
- Affecting upper body, neck and face > lower body
- Myalgia, dyspnea, hypotension

Management

- Stop infusion
- Administer antihistamine (diphenhydramine)
- Can restart at slower rate once symptoms resolve

Lincosamides

- **Clindamycin**
- Binds to the 50s ribosomal subunit of bacteria disrupting protein synthesis; **bacteriostatic**
- **Coverage:**
 - Anaerobic, streptococcal, & staphylococcal infections
 - **Antitoxin** effect against toxin-elaborating streptococci and staphylococci
 - Vancomycin doesn't stop the toxin production of Staph & Strep, therefore you should give Clindamycin with it in case of very ill patients
- **Usage:**
 - Bone/Joint and skin/soft tissue infection including MRSA
 - Pharyngitis, group A streptococci (eradicates the Chronic carrier treatment)
 - Toxic shock syndrome → To stop toxin production
 - Aspiration pneumonia
- **Side Effects:**
 - The most common side effect is **diarrhea**.
 - It's the most common cause of **C-difficile colitis**



Macrolides

- **Azithromycin, Erythromycin, Clarithromycin**
- Binds to the 50s ribosomal subunit of bacteria disrupting protein synthesis; bacteriostatic
- **Coverage:**
 - gram-positive bacteria (streptococci, staphylococci) and atypical bacteria, **Bordetella pertussis**.
- **Usage:**
 - Common substitute for patients with a **penicillin allergy**
 - **Pertussis**
 - Atypical pneumonia

- Side Effects:
 - Common side effect in neonates is **hypertrophic pyloric stenosis**

Metronidazole

- It inhibits nucleic acid synthesis by disrupting the DNA Synthesis; bactericidal
- **Coverage:** Anaerobic bacteria and protozoa
- **Usage:**
 - Clostridium difficile infection
 - Aspiration pneumonia
 - Intra-abdominal infections
 - lung abscess
 - Amoebiasis

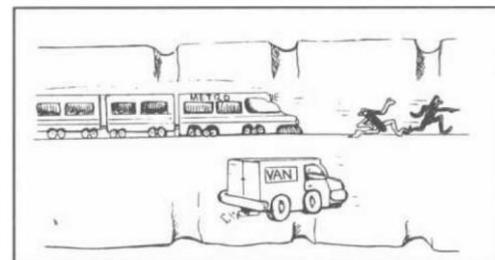


Figure 17-6

Fig. 17-6. Visualize a VAN (vancomycin) and a METRO (metronidazole) cruising down the GI tract. They run over the ulcerative potholes of pseudomembranous colitis and kill the offending *Clostridium difficile*.

Trimethoprim-sulfamethoxazole (bactrim)

- Inhibits **folate** biosynthesis and metabolism, **bactericidal**
- **Coverage:** Gram negative and most gram positive (MRSA), no coverage for group A strep
- **Uses:**
 - **Urinary tract infections**
 - Skin/soft tissue and bone/joint infections
 - Treatment and prophylaxis of **Pneumocystis jirovecii pneumonia (PCP)**;
 - **Shigella**
 - Treatment of **Stenotrophomonas maltophilia**
 - *Stenotrophomonas maltophilia* is an aerobic gram-negative bacillus. It is an uncommon pathogen in humans. It is usually incapable of causing disease in healthy hosts without the assistance of invasive medical devices that bypass normal host defenses. It's associated with pulmonary infections in **Cystic Fibrosis** patients.
- Sides Effects:
 - Not used in **G6PD** (causes hemolysis)
 - Not used in **neonates** (displaces Bilirubin)

Aminoglycosides

- Gentamicin, tobramycin, amikacin, neomycin, kanamycin, streptomycin
- Not available orally
- Binds the 30S ribosomal subunit inhibiting protein synthesis.
- Depending on their concentration, they act as bacteriostatic or bactericidal agents
- **Coverage:**
 - **Gram-negative** aerobic bacteria, including **pseudomonas**
 - **Gram positive** usually as **synergistic** effect.
 - The synergistic effect between **aminoglycosides** and **β-lactam** antibiotics is well established against gram positives
- **Use:** Usually used for **synergy** (G+ve) or **double** coverage (G-ve), or for **UTI**
- Side Effects:
 - **Ototoxicity** and **nephrotoxicity**

Aminoglycosides bind to **30S** ribosomal subunit

Macrolides and Lincosamides “Clindamycin” bind to **50S** ribosomal subunit

Anti specific

- Anti-pseudomonas
 - Aminoglycosides, quinolones, cephalosporins (ceftazidime, cefepime), antipseudomonal penicillins, carbapenems, polymyxins, monobactams (aztreonam)
- Anti-Anaerobic
 - metronidazole, clindamycin, carbapenem,
 - penicillin (i.e. ticarcillin, ampicillin, piperacillin) and a beta lactamase inhibitor (i.e. clavulanic acid, sulbactam, tazobactam),
- Anti-Atypical
 - Macrolides and Tetracyclines
- Anti-MRSA
 - Vancomycin, Linezolid, Lincosamides “Clindamycin”
 - ceftaroline
 - Bactrim, Doxycycline
- Anti-C.diff
 - Vancomycin & Metronidazole

Notes

- MCC of **skin infections** is **staph aureus** (staph aureus infections are rapid acute and life threatening)
- MCC of infections associated with **foreign bodies** (central line, vp shunt, foley's catheter) is **staph epidermidis** (it causes gradual indolent not life threatening infections)
- Beta hemolytic group A strep pyogenes “**GAS**” causes impetigo and scarlet fever
- Beta hemolytic group B strep agalactiae “**GBS**” causes neonatal infections (neonatal sepsis, neonatal meningitis)
- The resistance rate of group A and group B beta hemolytic strep to penicillins (penicillin, amoxicillin, ampicillin) is **zero!** So NO need for 2nd or 3rd line treatment for infections caused by these bacteria. the **DOC** is always **penicillin!** As in **tonsillitis** caused by group A strep. Or in **neonatal sepsis** caused by strep agalactiae (group B strep) where the DOC is **IV ampicillin or penicillin G (benzylpenicillin) (IV route)**
- **Strep pneumonia** infections have 2nd and 3rd line treatments because they may have resistance to penicillins ⇒ Ceftriaxone (Rocephin)
- **Strep. Viridans** (viridans means green) : it is most of the time just a contamination of blood, except in two cases
 - 1-if the patient has heart disease that predispose him for **infective endocarditis** (strep viridans is the most common cause of Inf.endocarditis in children)

- 2- if the patient is **immunocompromised** (chemotherapy) → sepsis.
- MCC of **UTI** infections is **E.coli**, but the most common gram positive infection of UTI is **enterococcus**.
- **Staph saprophyticus** is a cause of **UTI** infection in **sexually active** females adolescents.
- When A.Fleming discovered penicillin, the staph aureus was sensitive to it. But later on it built resistance by producing **penicillinase** which destroyed the penicillins. To overcome this resistance they added β lactamase inhibitors to the penicillins, such as clavulanic acid, and made new synthetic PCNs such as oxacillin which are penicillinase resistant. but then emerged MRSA (methicillin resistant staph.A) which has another mode of resistance by changing the PBP (**penicillin binding protein**; where the penicillin bind to the bacteria)
- **Staph aureus** is the most common cause of **skin, soft tissue, bone and joint infections** (septic arthritis , osteomyelitis, cellulitis) and it is the 2nd most common cause of central line infections after Staphylococcus epidermidis
- In **hospital acquired infections** we think of **MRSA, pseudomonas, acinetobacter** and other multi drug resistant bacteria.
- **Anaerobes** causes **aspiration pneumonia** (the patient aspirates abdominal content).
- **Atypical bacteria** is the most common cause of pneumonia in school age children (> 5 yrs old) and it is called **walking pneumonia** as it is mild so the patient doesn't stay in bed and comes walking, also there will be diffuse infiltrate on CXR. We treat it with **macrolides** and if the patient is old enough we may use **tetracycline** or **fluoroquinolone** in adults. (we don't give cell wall inhibitors Antibiotics such as penicillin because atypical bacteria doesn't have a cell wall)
- **Tetracycline** isn't given for children **under 8 yrs** because it causes permanent staining of teeth and joints.
- **Fluoroquinolones** are not used for **<18 years** old patients, because they affect growing cartilage and can cause tendon rupture .
- There is only one indication where we have to use **doxycycline** even in one year old child.
 - it is spotted **Rocky Mountain fever** (tick borne) and **rickettsial diseases**.
- We may use aminopenicillin like amoxicillin, or 1st generation cephalosporin for **E.coli** and **proteus UTI** infections but only as **targeted** therapy not as empiric therapy.
- **Actinobacter** is a multidrug resistant it's only treated by **colistin** and sometimes it's **pan-drug resistant** meaning that no drug in the world can treat it!
- **Moraxella** and **H.influenza** are the 2nd and 3rd most common causes of **pneumonia** and **sinusitis** and **otitis media** after strep.pneumonia
- **2nd and 3rd generation cephalosporins** are not affected by β -lactamase so we can give them in case of β -lactamase producing bacteria such as moraxella catarrhalis and h.influenza.
- The only time vancomycin is given orally is in c.difficile colitis (as a 2nd choice after metronidazole) because it can't be absorbed from the intestine.

- The main three causes of meningitis beyond the neonatal period are: **strep. Pneumonia, haemophilus, and N.meningitidis**. So the empiric therapy for meningitis is **vancomycin** and **ceftriaxone**.
- **Red man syndrome** caused by **vancomycin** is characterized by redness and itchiness of the whole body. The mechanism of action is direct stimulation of mast cells by vancomycin. and the histamine released causes inflammation. So we give antihistamines prior to vancomycin and we increase the infusion rate of the drug to over 2 hours instead of 30 minutes so it will be slow to hit the mast cells.
- The main use of **aminoglycosides** is for gram (-) bacteria. we use it in **gram positive** bacteria too but only in **synergy** with **b lactams** antibiotics (b lactams destroy the cell wall then aminoglycoside enters and inhibit synthesis of proteins)
- Double coverage means the use of more than one type of antibiotics in serious infections so if one type doesn't work the other may work.
- Tonsillitis DOC → amoxicillin
- Otitis media DOC → amoclan
- **G-ve → pink** \ **G+ve → blue**
- Oral Anti MRSA → clindamycin \\ IV Anti MRSA → clindamycin + vancomycin

Source: Dr. Dawood yusef lecture

Mohammed Nawaiseh

Neurology

- Anterior fontanelle is small in microcephaly and large in hydrocephalus.
- Tandem walking: 1st function to be lost in alcoholic cerebellar cortical degeneration.
- Brudzinski's sign is more sensitive than rigidity sign in meningism.
- **Developmental milestones:**
 - At birth: oriented to mother's smell.
 - 2 months: recognition of mother's voice.
 - 4 months: recognition of mother's face.
 - 2 months: 180° view in visual field.
 - 3 years: identification of 1ry colors. Before this age, they enjoy colors but can't identify them.
- Sensory function (temperature, pain and touch): very early development (at 25 weeks gestational age).
- After 32 weeks: coordination between sucking and swallowing.
- Sweat taste increases the heart rate, any other taste decreases the heart rate.
- Hearing is more advanced than vision.
- After age of 6 months: visual acuity as adults.
- 9th, 10th and 11th cranial nerves are mature at gestational age of 32 weeks.
- Motor exam: tone/ power/ muscle bulk/ involuntary movements.
- Both hypotonia and hypertonia can cause muscle wasting.
- Cerebellar disorder (hypoplasia) is one of causes of hypotonia.
- Absent Moro reflex at 1 month or delayed absence (after 9 months for example): indication of severe brain damage.
- Deep tendon reflexes present at birth.
- Babinski sign: normal up to 1.5 yr. but asymmetry is abnormal!
- Vibration: at birth.
- Proprioception: at 2 years.
- **Posture:**
 - Normal posture at birth: flexion position.
 - Abnormal postures:
 - ✓ Decorticate: flexion of upper limbs and extension of lower limbs/ damage of supratentorial structures.
 - ✓ Decerebrate: full extension/ brainstem damage.
 - ✓ Flaccid posture: brainstem + supratentorial damage.

- **Gait:**
 - Waddling gait: proximal weakness.
 - High steppage gait: distal weakness.
 - Scissoring gait: UMNL (pyramidal tract).
 - Shuffling gait: Parkinson.
 - Wide based gait: cerebellar disease.
 - Ataxic gait.
- Cerebellum function: targeting and alternating.
- Basal ganglia function: unconsciously executed functions (driving, walking, writing).

WEAKNESS AND HYPOTONIA – neuromuscular disorders

(nelson essentials, Dr. slides)

- Weakness is a decreased ability to voluntarily and actively move muscles. This may be generalized or localized to one aspect of the body.
- Hypotonia is a state of low muscle resistance to movement.

ETIOLOGY

- Weakness and hypotonia may be due to disorders of **upper motor neurons** or **lower motor neurons**.
- **Upper motor neurons** originate in the cerebral motor cortex; their axons form the corticospinal tract ending in the spinal cord and control voluntary motor activity.
- The anterior horn cells, their motor roots, peripheral motor nerves, neuromuscular junctions, and muscles represent **the lower motor neurons and muscle units**.
- Maintenance of normal strength, tone, and coordination requires integrated communication throughout this complex system, including the cerebral cortex, cerebellum, brainstem, thalamus, basal ganglia, and spinal cord.

DISEASE OF THE UPPER MOTOR NEURON

- Tumors, trauma, infections, demyelinating syndromes, infarction, metabolic diseases, and degenerative diseases may injure the corticospinal tract, producing an **upper motor neuron pattern of weakness coupled with increased deep tendon reflexes, spasticity, and extensor plantar responses (Babinski sign)**.
- The distribution of weakness depends on the location of the lesion.
- A tumor in the left parietal region may produce a right hemiparesis.
- A brainstem glioma may produce a slowly progressive quadriparesis.
- A diffuse disorder of myelin synthesis, such as a leukodystrophy, would produce a progressive symmetrical quadriparesis.

DISEASES OF THE SPINAL CORD

- Infarction or compression
- ***Acute or subacute flaccid paraparesis is either an acute cord syndrome or Guillain-Barré syndrome.***
- The hallmarks of spinal cord disease are a *sensory level, a motor level, disturbance of bowel and bladder function, and local spinal pain or tenderness.*

The acute cord syndrome

- May be the result of transverse myelitis, cord tumor, infarction, demyelination, or trauma.
- **Transverse myelitis, an acute post-infectious demyelinating disorder of the spinal cord, is treated with high-dose steroids.**

How do patients with peripheral nervous system disorders present?

- **Age of onset**: any age even intrauterine.
- Hypotonia, muscle weakness, gait abnormality
- **Family history** is usually positive (all modes of inheritance).

- Past history of possible respiratory infections and difficulties and feeding difficulties.
- Commonly motor delay.
- Rarely cognitive delay.
- Possible ocular muscle weakness
- History of NICU admission after birth.

How do patients with lower motor neurone disorders present?

- Cranial nerves: 3-7 and 9,11-12 are variably affected.
- Muscle weakness can be proximal, distal, ocular...
- Hypotonia and muscle wasting
- Tongue fibrillation in SMA
- DTR, superficial and primitive reflexes are depressed or absent.
- Babinski negative.
- Sensory is affected in neuropathies.
- Coordination is affected by the muscle weakness

How to investigate lower motor neurone disorders?

- CPK: high in muscle diseases.
- Nerve conduction study - NCS: abnormal in neuropathies axonal and demyelinating.
- EMG
 - Myopathic (low amplitude, short duration MUP, good recruitment).
 - Neurogenic (high amplitude, long duration, poor recruitment).
- Repetitive stimulation in Myasthenia Gravis.
- Muscle biopsy: immunohistochemistry and electron microscopy.
- Genetic: PCR, whole exome sequencing, next generation sequencing.

DISEASES OF THE LOWER MOTOR NEURON

- Any component of the lower motor neuron unit.

Anterior horn cell	Spinal muscular atrophy Poliomyelitis
Peripheral nerve	Guillain-Barré syndrome Hereditary motor sensory neuropathy Tick paralysis Bell palsy
Neuromuscular junction	Myasthenia gravis (juvenile, transient neonatal, congenital) Botulism
Muscle	Muscular dystrophies (Duchenne, Becker, limb-girdle) Myotonic dystrophies Congenital myopathies Metabolic myopathies Dermatomyositis Polymyositis

ANTERIOR HORN CELL

- Profound muscle weakness
- Muscle atrophy
- Diminished DTR
- Muscle fasciculations
- EMG: Neurogenic Changes

- NCS: normal or slight decrease in velocity

Classification of Anterior horn cell diseases :

A. Degenerative:
1.Spinal muscular atrophy (in details)
2.Infantile neuronal dystrophy
3.Arthrogyposis multiplex congenital
B. Infectious:
1.Poliomyelitis
2.Transversemyelitis
3.Neuromyelitis optica
C .Congenital
1.Diastematomyelia
2.Syringomyelia
3.Hydromyelia
D. Metabolic:
1.GM2
2.Glycogen Storage
3.Organic acidemia, hyperglycinemia
E .Vascular-Trauma
1.Ant.spinal art. Occlusion
2.spinal cord vascular anomalies

-Spinal Muscular Atrophy SMA (high yield)

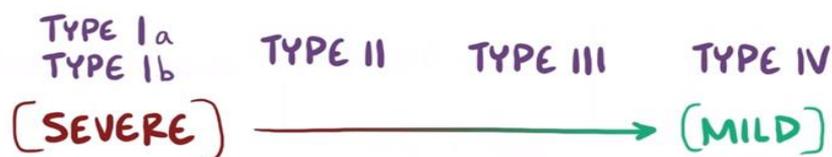
- 4 types
- Molecular basis chromosome region 5q13
- Progressive degeneration of **anterior horn cells**
- AR Genetic disease that may begin in intrauterine life or any time thereafter.
- About 25% of patients have a **severe** infantile form (SMA type1/Werdnig-Hoffmann disease)
- 50% have a **late infantile and slowly progressive** form (SMA type 2/Kugelberg-Welander syndrome),
- 25% have a more **chronic, juvenile form** (SMA type 3).
- **The earlier in life the process starts, the more severe the progression.**
- Infants with SMA type 1 present in early infancy with severe hypotonia, generalized weakness, and facial involvement.
- Infants have normal cognitive, social, and language skills and sensation.
- **Fasciculations** (quivering of the lateral aspect of the tongue)
- Deep tendon reflexes are absent.

- With progression, breathing becomes rapid, shallow, and predominantly abdominal. Respiratory compromise leads to atelectasis, pulmonary infection, and death.
- Most infants with SMA type 1 die within the first 2 years.
- Children with SMA type 2 may survive to adulthood.
- Children with SMA type 3 can appear normal and have normal life expectancy.

➤ Type I SMA Werdnig-Hoffman most severe
◦ -age of onset 3 rd trimester-6 months
◦ -usually die before age of 2 years
◦ -8% can live upto age of 10 years
• Type II SMA intermediate type
◦ onset after 6 months
◦ never walk
➤ Type III SMA: Kugelberg-Welander
◦ IIIa : onset before 3 years of age , IIIb: onset after 3 years of age
◦ Both are able to stand and walk
◦ Wheelchair-bound during early adulthood
• Type IV SMA -age of onset after age of 21yrs.
➤ Type 1A SMA (type zero)
◦ severe, antenatal-birth onset, arthrogryposis, death before 6 months
➤ Type non-5q13 SMA (AD, x-linked, recessive....)

SMA Cont.

- Investigations:
- Genetic testing.**
- Creatine phosphokinase (CK) may be **normal or mildly elevated.**
- The electromyelogram (EMG) shows **fasciculations, fibrillations, and other signs of denervation.**
- Muscle biopsy** specimens show grouped **atrophy.**
- Treatment
- No specific treatment delays progression.
- Symptomatic therapy** - minimizing contractures, preventing scoliosis, maximizing nutrition, and avoiding infections.
- Somatic gene therapy seems likely in the near future, the aim is to restore full length SMN II RNA/protein**



LMN - Peripheral Neuropathy

Anterior horn cell	Spinal muscular atrophy Poliomyelitis
→ Peripheral nerve	Guillain-Barré syndrome Hereditary motor sensory neuropathy Tick paralysis Bell palsy
Neuromuscular junction	Myasthenia gravis (juvenile, transient neonatal, congenital) Botulism
Muscle	Muscular dystrophies (Duchenne, Becker, limb-girdle) Myotonic dystrophies Congenital myopathies Metabolic myopathies Dermatomyositis Polymyositis

- Distal weakness , high-steppage gait.
- Diffuse, segmental, dermatome, sensory changes
- DTR is usually absent.
- Focal weakness , foot drop.
- Distal ulcers.

Peripheral nervous system:

1.cranial nerves 2.spinal roots 3.plexuses 4.peripheral nerves 5.autonomic ganglia

Classified as:

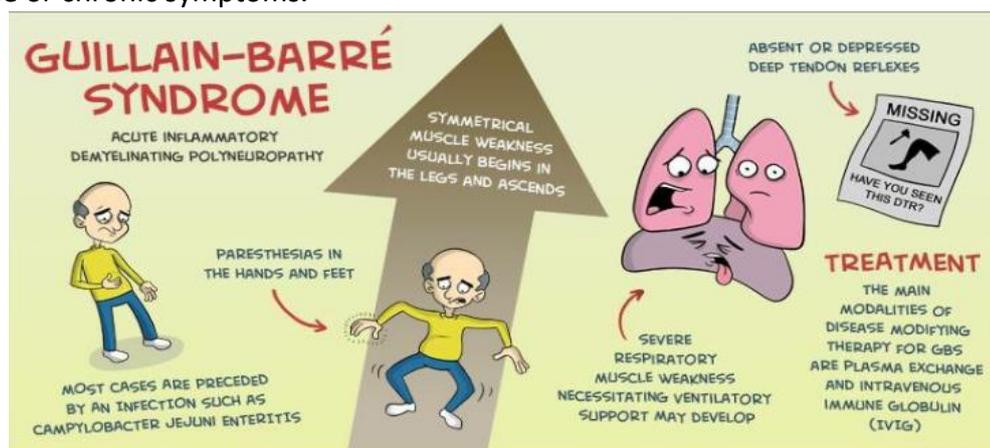
- Onset : Acute or chronic
- Function: motor, sensory, autonomic
- Distribution: radicular, demyelinating, axonal

1.Inflammatory: Gullian-Barre syndrome
2.Hereditary motor sensory neuropathies 4 types
3.Sensory neuropathies. 4 types
4.Congenital,inherited,metabolic:
<ul style="list-style-type: none"> ○ Congenital hypomyelinating ○ Infantile axonal dystrophy ○ Friedreich's ataxia ○ krabbes disease ○ Alpha-lipoproteinemia ○ metchromatic leukodystrophy ○ refsum disease ○ Chediak-Higashi ○ diabetic, uremic, acute intermittent porphyria ○ Thiamine deficiency & congenital pernicious anemia
5.Toxins-drugs:
<ul style="list-style-type: none"> ○ Diphtheria serum sickness ○ antibiotic induced ○ nitrofurantoin,ethambutol ○ pyridoxine induced ○ Nitrous oxide induced ○ antineoplastic drugs induced ○ vaccine induced ○ heavy metal induced

GuillainBarré Syndrome

A **post-infectious autoimmune** peripheral neuropathy that can occur about 10 days after a respiratory or gastrointestinal infection

- -Classically ***Mycoplasma pneumonia* or *Campylobacter jejuni***.
- -It occurs in people of all ages and is the **most common cause of acute flaccid** paralysis in children.
- symptoms - *areflexia, flaccidity, and symmetrical ascending weakness*.
- Progression can occur rapidly, in hours, or more indolently over weeks.
- Typically symptoms start with numbness or paresthesia in the hands and feet, then a heavy, weak feeling in the legs.
- **Weakness ascends to involve the arms, trunk, and bulbar muscles (tongue, pharynx, larynx).**
- DTR are **absent** even when strength is relatively preserved. sensory loss are usually minor.
- Bulbar and respiratory insufficiency may progress rapidly.
- Dysfunction of autonomic nerves can lead to BP changes, tachycardia , arrhythmias, urinary retention or incontinence, or stool retention.
- *This polyneuropathy can be difficult to distinguish from an acute spinal cord syndrome. loss of arm reflexes, absence of a sensory level, and lack of spinal tenderness point toward GBS.*
- A cranial nerve variant OF GBS called the **Miller Fisher variant** manifests with ataxia, partial ophthalmoplegia, and areflexia.
- The **CSF-** classically shows **elevated protein levels** MRI with gadolinium may reveal enhancement of the spinal nerve roots.
- Pulmonary and cardiac functions are monitored continuously.
- **TTT** - initially **(IVIG). Plasma exchange and immunosuppressive drugs** are alternatives when IVIG treatment is unsuccessful.
- The illness usually resolves spontaneously, albeit slowly; 80% of patients recover normal function within 1-12 months. 20% of patients are left residual weakness. Some will suffer acute relapse or chronic symptoms.



Chronic Inflammatory Demyelinating Polyneuropathy

- CIDP is an **immune-mediated** peripheral neuropathy and can affect patients of all ages.
- Patients present with both **proximal and distal weakness** an episodic, relapsing remitting pattern) affecting the extremities.
- Patients may also experience **sensation changes** such as numbness, tingling, or pain.
- The diagnosis is clinical.
- The treatment for CIDP are **IVIG, glucocorticoids, and plasmapheresis**.

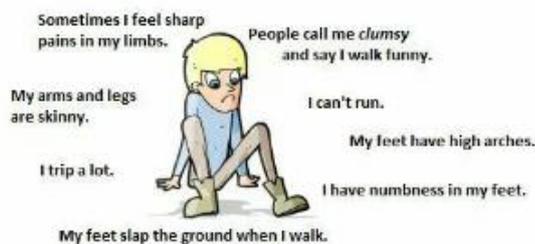
- Prognosis **varies**, with some patients undergoing complete remission, whereas others experience partial remission or severe disability.

Hereditary Motor Sensory Neuropathy (Charcot-Marie-Tooth Disease [CMT])

- Genetic loci : 26
 - Inheritance: AR, AD, X-linked.
 - Heterogeneity of the phenotypes and genotypes.
- a group of progressive **peripheral nerve diseases**.
 - **Motor components** generally dominate the clinical picture, with sensation and autonomic functions affected later.
 - The most common HMSN is CMT type 1A. Other forms may have milder symptoms.
 - The **peroneal and tibial nerves** are the earliest and most severely affected.
 - Most often, complaints begin in the preschool to early adolescent years, with **weakness of the ankles and frequent tripping**.
 - Examination shows **pes cavus deformity of the feet** (high-arched feet), bilateral weakness of foot dorsiflexors, and normal sensation despite occasional complaints of paraesthesia.
 - Peripheral nerves can become **enlarged and may be palpable on exam**.
 - Progression of HMSN is slow, extending over years and decades.
 - Some patients never have more than a mild foot deformity, loss of ankle reflexes, and electrophysiologic abnormalities.
 - Others in the same family may be confined to a wheelchair and have difficulties performing everyday tasks with their hands.
 - HMSN can be either **demyelinating** (CMT1, with severely decreased NCV and hypertrophic changes on sural nerve biopsy) or **axonal** (CMT2, with normal NCV but decreased action potential amplitudes and axonal degeneration on biopsy).
 - Genetic testing is available.
 - Specific treatment for HMSN is not available, but braces that maintain the feet in dorsiflexion can improve function.



Symptoms of CMT can include



Tick Paralysis

- Tick paralysis produces an acute lower motor neuron pattern of weakness, clinically similar to GBS.



- An attached female tick releases a toxin, similar to botulism, blocking neuromuscular transmission.
- Affected patients present with a severe generalized flaccid weakness, including ocular, papillary, and bulbar paralysis.
- A methodical search for an affixed tick, particularly in hairy areas, must be made in any child with acute weakness.
- Removal of the tick results in a prompt return of motor function.

Neuromuscular junction

Anterior horn cell	Spinal muscular atrophy Poliomyelitis
Peripheral nerve	Guillain-Barré syndrome Hereditary motor sensory neuropathy Tick paralysis Bell palsy
→ Neuromuscular junction	Myasthenia gravis (juvenile, transient neonatal, congenital) Botulism
Muscle	Muscular dystrophies (Duchenne, Becker, limb-girdle) Myotonic dystrophies Congenital myopathies Metabolic myopathies Dermatomyositis Polymyositis

Myasthenia Gravis

A. Immune mediated:
1.transient neonatal
2.Juvenile
3.adult onset
B. Non-immune mediated
1.familial infantile myasthenia
2.congenital paucity of synaptic vesicles
3.Fast & slow channel syndromes
4.Cong.endplate AchE deficiency
5.Deficiency & short open time of AchR
6.Abnormal interaction of Ach with AchR
7.Cong.AchR deficiency
8.Cong.AchR & AchE dediciency

- Myasthenia gravis is an autoimmune condition.
- Most commonly, ABs block the acetylcholine receptors (AChR) at the NMJ, which results in rapid fatigability of striated muscle.
- Childhood varieties are **juvenile myasthenia gravis** in late infancy and childhood, **transient neonatal myasthenia**, and **congenital myasthenia**.
- **Juvenile Myasthenia: Comprise 10-20% of all MG.**
- Variable ptosis, diplopia, ophthalmoplegia, and facial weakness
- Dysphagia, poor headcontrol, and extremity weakness may occur. Rapid fatigue of muscles distinguishes myasthenia from other NM disorders, with progressive worsening over the day or with repetitive activity.
- TTT- includes **pyridostigmine**, an inhibitor of acetylcholinesterase.

- Ocular MG is more common in children than generalized which can present as unilateral or asymmetric (curtain sign).
- Children tend to have neck flexion weakness (<10 yrs).
- **Transient Neonatal Myasthenia Gravis:**
- Develops in 10% to 20% of neonates born to mothers with myasthenia gravis
- Presenting in the first hours to days after birth.
- Almost all infants born to mothers with MG have maternal anti-AChR ABs.
- Ptosis, ophthalmoplegia, weak facial movements, poor feeding, hypotonia, respiratory difficulty, and variable extremity weakness.
- Neonates with transient myasthenia gravis require cholinesterase inhibitors and supportive care for a few days to weeks until the weakness remits.
- **Congenital Myasthenia Gravis** not autoimmune mediated.
- Abnormality is pre, post and synaptic, while in immune MG ,abnormality is mainly, post-synaptic.
- Gene mutations in the components of the NMJ.
- hypotonia, ophthalmoparesis, facial diplegia, and extremity weakness, lifelong disability. Some children will respond to pyridostigmine, others unresponsive.

Diagnostic Studies MG

- **Clinical symptoms** and **antibody testing**.
- The majority have antibodies to the **AChR**, although some have antibodies to other components of the NMJ.
- Neurophysiology may exhibit the classic feature of electrodecrement **with 3-Hz repetitive stimulation** during nerve conduction studies.
- Administration of a cholinesterase inhibitor (**edrophonium chloride**) can result in transient improvement in strength, particularly of ptosis, *additionally be used for diagnostic verification*.

MG associated disorders Hyper-hypo thyroidism, RA,SLE,Pernicious anemia Glomerulonephritis, IBD, Sarcoidosis, Myotonic dystrophy and other myopathies, Cardiac disorders

Neuromuscular junction

Infant Botulism

- Results from intestinal infection by *Clostridium botulinum*,
- which produces a neurotoxin that blocks **presynaptic cholinergic transmission**.
- Young age and the absence of competitive bowel flora predispose infants to this disease.
- Infants may ingest dust, soil, or food (**honey or poorly canned foods**) contaminated with spores.
- The progressive neuromuscular blockade ranges from mild to severe. Infants often present with constipation and poor feeding. Hypotonia and weakness develop.
- Cranial nerve dysfunction manifested by decreased gag reflex, diminished eye movements, decreased pupillary contraction, and ptosis. HR and BP may fluctuate. Affected infants may develop respiratory failure.
- The diagnosis is made by the presence of *C. botulinum* spores and toxin in stool samples.
- TTT- IVIG should be administered as soon as the diagnosis is suspected.



Eaton-lambert syndrome:

- Acquired immune-mediated presynaptic NMJ disorder
- paraneoplastic or non paraneoplastic.
- Transient neonatal ELS has been reported. It is rare in children

Muscles weakness-

Anterior horn cell	Spinal muscular atrophy Poliomyelitis
Peripheral nerve	Guillain-Barré syndrome Hereditary motor sensory neuropathy Tick paralysis Bell palsy
Neuromuscular junction	Myasthenia gravis (juvenile, transient neonatal, congenital) Botulism
Muscle	Muscular dystrophies (Duchenne, Becker, limb-girdle) Myotonic dystrophies Congenital myopathies Metabolic myopathies Dermatomyositis Polymyositis

A.congenital myopathies (in details)
B.Dystrophies:
◦ 1.Congenital MD (in details)
◦ 2.Dystriphinopathies
◦ 3.Limb-girdle MD (sarcoglycanopathies)
◦ 4.Myotonic MD
◦ 5.Facio scapula-humoral MD
◦ 6.Emery-Dreifus MD
◦ 7.Oculo-paryngial MD
C. Mitochondrial myopathies
D. Inflammatory myopathies
E. Endocrine myopathies
F. metabolic myopathies
G. distal Myopathies

Clinical presentation of myopathies

Perinatal:

- Decrease fetal movements, hypotonia and weakness, feeding and respiratory difficulties pes cavus and contractures.

Infants:

- Hypotonia, proximal weakness, recurrent chest infections, seizures and coma (mitochondrial and metabolic),endocrine changes (endocrine disorders), Cardiac symptoms.

Children:

- The above and waddling gait ,pseudohypertrophy, muscle wasting and sign, muscle cramps.

Congenital myopathy

Clinical Course:

- Usually non-progressive muscle weakness and hypotonia
- Nondystrophic muscle disorders
- Some infants have progressive course leading to death.
- Occasionally do not manifest until later in childhood or even adulthood.

- Rarely, demonstrate clinical improvement
- ASSOCIATED with: High arched palate, pectus excavatum, kyphoscoliosis and dislocated hips.
- 40 types.
- Have characteristic morphological features in skeletal muscles superimposed by type I myofiber predominance and atrophy. Such morphological features may coexist with other muscle diseases changes.
- CPK: normal
- EMG: normal or mildly myopathic
- Ttt: supportive.

Congenital muscle dystrophy

- Presentation at birth-first year of life
- The most common subtypes include **merosin- deficient congenital muscular dystrophy**, Ullrich congenital muscular dystrophy, and dystroglycanopathies.
- **Classification:**

• Mutation in the genes of: laminin alpha 2, collagen, integrin, dystroglycan 1.
• Forms secondary to genes encoding glycosyl transferases that affect alpha dystroglycan: fukuyama, muscle eye brain disease, walker-Warburg MDC1C and MDC1D, and others.
• Defects of nuclear envelope proteins (LMNA and nesprin)
• Defects in the protein related to endoplasmic reticulum ex. rigid spine syndrome (SEPN1 gene mutations).
• CMD with mitochondrial structural abnormalities.

- **Clinical features** include hypotonia, extremity weakness, delayed motor development and congenital contracture.
- **Diagnosis** elevated serum CK and dystrophic changes on muscle biopsy.
- In most individuals, the disease course is slow or nonprogressive
- Contractures and scoliosis are often progressive and severely worsen; respiratory status diminishes with age.
- **Treatment-** Potential role of antioxidants N-acetylcysteine.

Dystrophinopathies (high yield)

- Duchenne, Becker MD, X-linked dilated cardiomyopathy
- Genetics
- 70% have deletion or duplication in dystrophin gene.
- If screen is –ve then go for muscle biopsy.
- Females with dystrophin mutation have MD if there is abnormality of X inactivation or chromosomal anomaly XO.

Symptoms and signs in DMD & BMD carriers

Clinical features	DMD carries	BMD carries
Myalgia/cramps	5 %	5 %
Muscle weakness	19%	14%
No symptoms/signs	76%	81%
Left ventricular dilatation	19%	16%
Dilated cardiomyopathy	8%	0

Duchenne Muscular Dystrophy

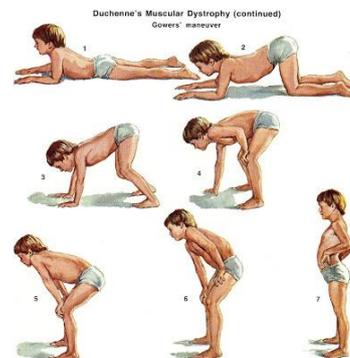
- Group of genetic muscle diseases characterized by progressive **myofiber degeneration**, + gradual replacement of muscle **by fibrotic tissue**.
- Duchenne muscular dystrophy is the **most common muscular dystrophy**
- X-linked disorder (Xp21) affecting approximately 1 in 3500 boys and resulting from **a gene mutation of dystrophin**.

Becker muscular dystrophy

- allelic disorder associated with more mild symptoms; its mutations partially preserve the function of the resulting gene product.

Clinical manifestation of muscular dystrophy:

- Infant boys are only rarely symptomatic in early infancy.
- At about 2 to 3 years of age, boys develop an inability to run properly.
- Some have an antecedent history of mild slowness in attaining motor milestones or poor head control during infancy.
- Examination shows **firm calf hypertrophy** and mild to moderate proximal leg weakness with a hyperlordotic, waddling gait.
- The child typically arises from a lying position on the floor by using his arms to *climb up* his legs and body (**Gower sign**).
- Arm weakness is evident by age 6 years, and most boys are wheelchair dependent by age 12 years.
- Other manifestations include **cardiomyopathy**, scoliosis, respiratory decline, and, in some boys, cognitive and behavioural dysfunction.
- Many boys with Duchenne live into adulthood. Most die in their 20s or early 30s, usually as a result of **respiratory decline or cardiac dysfunction**.



Laboratory and Diagnostic Studies

- Serum **CK levels** are always markedly **elevated**.
- Diagnosis - genetic testing for the **dystrophin gene mutation**.
- Prenatal diagnosis is possible.
- **Occasionally, the diagnosis is not made until a muscle biopsy shows muscle fiber degeneration and regeneration accompanied by increased intrafascicular connective tissue.**
- TTT-**Steroid therapy** *slow the pace of the disease & delay motor disability*.
- Supportive care includes physical therapy, bracing, proper wheelchairs, and treatment of cardiac dysfunction or pulmonary infections.

Limb Girdle muscle Dystrophy (LGMD)

- Heterogenous group

A. Dominant form LGMD1 (mild)

B. Recessive form LGMD 2 (severe)

- Onset of symptoms: rare in childhood and common in adolescent or early childhood period.
- A subset of children will have a **Duchenne-like presentation**.
- LGMD primarily affects muscles of the **hip and shoulder girdles**.
- Distal muscles may later become weak and atrophic.
- Many children with LGMD will **lose the ability to ambulate**. Some may also have progressive cardiac and respiratory failure.
- **Immunostaining** is diagnostic in most cases, **15%** have **dystrophin** mutations.

Fascioscapulothoracic MD

- Facioscapulothoracic dystrophy is an AD myopathy
- Wide spectrum of weakness, first appears in the facial and shoulder girdle muscles.
- Shoulder weakness results in the characteristic observation of scapular winging, which can often be asymmetric
- Hearing loss.
- Majority have normal IQ but mental retardation and seizures in severe cases.
- A dominant and deletion is present in long arm of chromosome 4.
- Patients have mild ptosis, a decrease in facial expression, inability to pucker the lips or close eyes during sleep, and thinness of upper arm musculature.
- Disability related to upper extremity weakness and dysfunction.



Myotonic dystrophy

- Two types 1 and 2
- An AD genetic disease, DM is caused by progressive expansion of a triplet repeat, **CTG**, in the myotonic dystrophy protein kinase gene. (**DMPK**)
- Presentation is roughly **correlated** with the number of CTG repeats.
- Disease is characterized by **genetic anticipation**, where each generation presents with earlier and **more severe symptoms**.
- Clinically indistinguishable but DM2 is milder.
- Severe DM1 have cognitive impairment. Smooth muscle involvement and central hypersomnolence are troublesome.
- Slowly progressive **facial and distal extremity weakness** as well as **myotonia**. *Myotonia is a disorder of muscle relaxation after contraction. Patients grasp onto an object and have difficulty releasing their grasp, peeling their fingers away slowly.*
- The facial appearance is characteristic, with hollowing of muscles around temples, jaw, and neck; ptosis; facial weakness; and drooping of the lower lip.

- Not only is the striated muscle affected, but **smooth muscle of the alimentary tract, uterus, and cardiac tissue are involved**. Patients have variable arrhythmias, endocrinopathies, immunologic deficiencies, cataracts, and intellectual impairment.

Emery Dreifuss MD *humero-peroneal muscular dystrophy*

- inherited as an X-linked recessive, AD, or AR disorder
- X-linked more common (emerin protein) A dominant (lamin A/C) gene
- Both proteins related to nuclear membrane
- **Early contractures of outproportion to weakness.**
- Symptoms typically begin in childhood
- slowly progressive **humero-peroneal muscle weakness** or wasting, and cardiac disease with conduction defects and arrhythmias.
- mild **elevations of serum CK levels**, abnormal (ECG), characteristic changes on muscle imaging, and abnormal but nonspecific muscle biopsies.
- There are no disease- specific modifying therapies, although early placement of defibrillators in patients with abnormal ECGs reduces the incidence of sudden death.



Metabolic myopathies *(dr slides only)*

- Mitochondrial encephalomyopathies
- Glycogen storage diseases
- lipid storage myopathies due to fatty acid oxidation disorders.

A.MITOCHONDERIAL Disorders

- Main abnormality is in the oxidative phosphorylation which is carried out in the inner mitochondrial membrane by the respiratory chain complexes I-IV and by the ATP synthase complex V.
- Complex II is encoded by nuclear DNA.
- Other complexes are encoded by either mitochondrial or nuclear DNA.
- Nuclear DNA includes 70 genes and mitochondrial DNA 13 genes.
- 50% of adult mitochondrial diseases and 80% of pediatric cases are due to nuclear gene defects.
- **No effective treatment.**
- **Metabolic:**
 - Creatine in some mitochondrial disorders
 - CoQ10: not effective in mitochondrial DNA-associated Mit.diseases but effective in COQ10 deficiency.
 - Idebenone (Quinone) good for Friedreich's ataxia.
 - thiamine, riboflavin, carnitine, vitamin E, arginine
- **Gene therapy:** successful in cultured cells.

Glycogen storage disorders (GSD)

- Two main clinical GSD syndromes:

1. Exercise intolerance, with cramps, and myoglobinuria.

These are generally associated with the following GSD:

- A. glycogenolysis; phosphorylase kinase and myophosphorylase deficiencies.

- B. Glycolysis; phosphoglucosaminase, phosphofructokinase, aldolase, betaenolase, phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase deficiencies.

2. progressive weakness involving limb and trunk muscles.

A. Glycogenosynthetic pathway: glycogenin and brancher enzyme deficiency.

B. lysosomal glycogenolytic system: acid mlatase deficiency

However, symptoms above have variations in their presentations and in the 2 groups.

C. Lipid storage myopathies due to fatty acid oxidation defects

A. Metabolic decompensation during fasting, infection, prolonged exercise, cold exposure and stress that may lead to coma, Reye like syndrome, sudden infant death syndrome, seizures.

B. tissues with high energy such as skeletal muscles ,heart, and liver are dependent upon efficient FA oxidation

- With deficient hepatic ketogenesis, glucose becomes the only available fuel during fasting, free fatty acids are liberated but can't be metabolized due to the block. so,they are stored as triglycerides which may lead to lipid storage in muscle ,heart and liver.

C. Hypoketotic hypoglycaemia due to the FA metabolism block and consumption of glucose.

D. Decrease in total carnitine concentration.

E. Dicarboxylic aciduria ,increase ammonia, acidosis, myoglobinuria....

Inflammatory Myopathies

- Most common form of acquired myopathy.
- Most of them are idiopathic and most common is dermatomyositis.
- Most common infectious myositis is viral.
- Known agents are influenza, toxoplasma, trichinosis and inclusion body myositis.
- Pathogenesis: dermatomyositis is an antibody mediated- systemic angiopathy and polymyositis is cell mediated disorder in which muscle is the target tissue.
- Risk of cancer is not increased in children.

Hypotonia without Significant Weakness (Central Hypotonia)

- Some infants who appear to move well when supine in their cribs are *floppy* when handled or moved. When lifted, their heads flop, they *slip through* at the shoulders, do not support weight on their legs, and form an *inverted U* in prone suspension (**Landau posture**).
- When placed prone as neonates, they may lie flat instead of keeping their arms and legs flexed. Passive tone is decreased, but reflexes are normal.
- Hypotonia may be associated with significant cerebral disease or may be a benign phenomenon that is outgrown.
- The most common cause of hypotonia is hypoxic-ischemic encephalopathy.
- **Prader-Willi syndrome (PWS)** presents with severe neonatal hypotonia; severe feeding problems leading to failure to thrive; small hands and feet; and, in boys, a small penis, small testicles, and cryptorchidism. Severe hyperphagia and obesity develop in early childhood. Approximately 60% to 70% of affected individuals have an interstitial deletion of *paternal* chromosome 15q11q13.

- PWS and trisomy 21 are the most common genetic causes of neonatal hypotonia.
- Infants who have a connective tissue disorder, such as **Ehlers-Danlos syndrome**, **Marfan syndrome**, or familial laxity of the ligaments, may exhibit marked passive hypotonia, *ligamentous laxity*, and increased skin elasticity.
- They have normal strength and cognition and achieve motor and mental milestones normally. They may have peculiar postures of their feet or unusual gaits.
- Infants with **benign congenital hypotonia** typically exhibit the condition at 6 to 12 months old with delayed gross motor skills. They are unable to sit, creep, or crawl, but have good verbal, social, and manipulative skills. Strength appears normal, and the infants can kick arms and legs briskly and bring their toes to their mouths. The children often display head lag, slip-through in ventral suspension, and floppiness of passive tone. The infant seems floppy from birth.

Table 182-4 Approach to Differential Diagnosis in the Floppy Infant	
HYPOTONIA WITH WEAKNESS	
<i>Awareness Intact</i>	
Neuromuscular disease	
Spinal muscular atrophy*	
Myasthenic syndromes	
Congenital neuropathy or myopathy	
Spinal cord disease (cervical cord trauma or compression)	
Tumor	
Spinal cord infarct	
Malformation	
Spina bifida	
Syringomyelia	
<i>Consciousness Depressed</i>	
Severe brain illness*	
Structural (hydrocephalus)	
Infectious	
Metabolic (e.g., anoxia or hypoglycemia)	
Intoxication through mother	
Magnesium sulfate	
Barbiturates	
Narcotics	
Benzodiazepines	
General anesthesia	
Metabolic abnormality	
Hypoglycemia	
Kernicterus	

HYPOTONIA WITHOUT WEAKNESS
Acute systemic illness*
Specific syndromes
Down syndrome*
Cerebrohepato renal (Zellweger peroxisomal disorder)
Oculocerebrorenal (Lowe syndrome)
Kinky hair disease (Menkes syndrome—copper metabolism disorder)
Neonatal adrenal leukodystrophy
Prader-Willi syndrome
Connective tissue disorder
Ehlers-Danlos syndrome
Marfan syndrome
Congenital laxity of ligaments
Nutritional-metabolic disease
Rickets
Renal tubular acidosis
Celiac disease
Biliary atresia
Congenital heart disease
Benign congenital hypotonia*

Done by: Esra'a Alkubaisi

Cerebral palsy

Source: Dr. Amira Masri slides and lecture notes

Cerebral palsy (CP) is a non-progressive (static) disorder of motor function and movement that usually manifests early in life as a result of central nervous system damage to the developing brain.

It is non-progressive regarding deterioration (no deterioration) but it does improve, except for spasticity which doesn't improve.

Epidemiology

- Most patients are identified by 2 years of age due to delayed motor milestones.
- Incidence is 1.5 to 2.5 per 1000 live births.
- Slightly higher prevalence in males M:F = 1.5:1
- Poor prenatal care may increase the incidence of cerebral palsy.

Causes and risk factors

1. Prenatal

- 70-80% cases are prenatal in origin.
- Although prematurity is the most common known antecedent of CP, the majority of children who develop CP are born at term.
- In most cases, the exact cause is unknown but is most likely multifactorial.
- 10% - 28% of cases are due to birth asphyxia in term and near-term infants.
- Maternal infections and fever: TORCH = responsible for 5% of CP cases
- Multiple gestations:
 - ✓ risk of having a child with CP is 0.2% for single births, 1.3% for twins, and 7.6% for triplets.
 - ✓ Weight discordance greater than 30% is associated with a 5-fold increased risk of CP.
 - ✓ Death of a co-twin or co-triplet is associated with a 10% and 29% risk of CP for the surviving twin or triplets, respectively.
- Placental pathology: thrombosis
- Maternal metabolic disturbances (DM type 1 or type 2 or thyroid abnormalities)
- Intrauterine exposure to toxins

2. Perinatal

- Hypoxia-ischemia: 6%
- Periventricular leukomalacia

- Fetal/neonatal stroke
- Hyperbilirubinemia

3. Postnatal

- Stroke / trauma / infection

Classification

1. According to limbs affected

- **Hemiplegic CP (33%)**
 - ✓ One side is affected, arm is more affected than leg
 - ✓ Patients walk on tip toes and swing the affected leg (semicircular arc)
 - ✓ Corticosensory impairment is common
 - ✓ Mental retardation in 1/3
 - ✓ Seizures in 1/3
 - ✓ Vision could be affected
- **Quadriplegic (6%)**
 - ✓ Generalized increase in muscle tone
 - ✓ All 4 limbs are affected, legs > arms
 - ✓ Opisthotonic posture (in first year of life)
 - ✓ Difficulties in swallowing and articulation
 - ✓ Incoordination of oropharyngeal muscle (recurrent pneumonia)
 - ✓ Seizures in 50%
 - ✓ Mental retardation in majority
 - ✓ Auditory and visual abnormalities are common
- **Diplegic (44%, most common)**
 - ✓ Bilateral leg involvement
 - ✓ Commonly some degree of UL involvement
 - ✓ Infant (scissoring), older child (tip toe walk)
 - ✓ Seizures , MR and visual abnormalities are common
- **Monoplegic (one limb affected)**

2. According to neurological dysfunction

- **Spastic**
 - ✓ most common type (70%-80%)
- **Ataxic**
 - ✓ Characterized by cerebellar dysfunction
 - ✓ Least common type (1%)
- **Dyskinetic**
 - ✓ (extrapyramidal, choreoathetoid): due to predominant basal ganglia involvement in patients with acute severe hypoxia and kernicterus.

- ✓ Athetosis: slow writhing involuntary movements and involves distal limbs.
- ✓ Choreiform movements: asymmetric, uncoordinated, involuntary muscle contractions.
- ✓ Symptoms consistent with a movement disorder may appear later in life: May not be apparent until about 12 to 18 months of age.
- ✓ More prominent under stress
- ✓ One known cause is very high bilirubin levels during the neonatal period
- ✓ Risk of deafness in those affected by kernicterus
- **Mixed**
 - ✓ Involves both symptoms of upper motor neuron lesion and extrapyramidal symptoms.
 - ✓ e.g. a child who has spastic quadriplegia may also have choreoathetoid movements.

3. Functional classification

- Class 1: practical limitation of activity
- Class 2: slight – moderate limitation
- Class 3: moderate to great limitation
- Class 4: inability to carry out any useful physical activity

Associated conditions

- Mental retardation: 30- 50%
- Ophthalmologic defects: 30%
- Hearing impairment: 10%
- Speech and language disorders :40%
- Epilepsy: 30- 40%

Pathophysiology

- Cerebral ischemia before 20th week of gestation = neuronal migration deficit (lissencephaly).
 - ✓ Lissencephaly = smooth brain
 - ✓ Convolutions of brain are formed before 3rd trimester, when ischemia do occur before 20th week, convolutions not formed and lissencephaly results.
 - ✓ Causes of cerebral ischemia: viral infection early in pregnancy/ insufficient blood supply to fetal brain/ in Jordan, most cases are hereditary, so maternal hypoxia is less likely to be the cause.

✓

- Cerebral ischemia 26th - 34th weeks = periventricular leukomalacia
- Cerebral ischemia 34th- 40th weeks = focal or multifocal cerebral injury
- Premature: the distribution of fetal circulation to the brain results in the tendency for hypoperfusion to the periventricular white matter >> germinal matrix hemorrhages or periventricular leukomalacia >> spastic diplegic presentation (if larger area = quadreplegic)
- At term: hypoperfusion mostly targets injury to the watershed areas of the cortex (e.g. end zones of the major cerebral arteries) = spastic quadriplegia, if middle cerebral artery affected >> spastic hemiplegic phenotype
- If basal ganglia affected >> extrapyramidal symptoms (e.g. choreoathetoid or dystonic)

Diagnosis (history and physical examination)

- The child is not losing function (the patient does not have a progressive disease)
- Presents with delayed motor milestones
- History is the most important in diagnosis
- Left or right handed feature appears after age of 1.5 year, if before this age, it is an indication of weakness in one limb >> clue for CP
- Examination: hypotonia, spasticity, persistent primitive reflexes, underdevelopment of parachute reflex
- Spasticity of upper limbs may not be noticed till 7 months of age
- Spasticity of lower limbs may not be noticed till 9-10 months of age
- No diagnostic lab test

Evaluation

- Neuroimaging: MRI is preferred to CT scanning because of the higher yield of suggesting an etiology and timing of insult leading to CP (MRI shows abnormality in 90%, CT in 77%)
- screen for: mental retardation/ Ophthalmologic impairments/ hearing impairments/ speech and language disorders
- Monitor for: Nutrition, growth and swallowing dysfunction
- Genetic and metabolic studies shouldn't be routinely obtained, consider doing it if:
 - ✓ history or neuroimaging do not determine a specific structural abnormality
 - ✓ atypical features in history or clinical exam
 - ✓ Detection of a brain malformation
- Testing for a coagulation disorder should be considered in hemiplegic CP (high incidence of unexplained cerebral infarction)
- EEG: not routine, should be obtained if history suggesting epilepsy

Management

- Multidisciplinary team: Physical therapy/ Occupational therapy/ Speech therapy/ Behavioral therapy/ Psychological counseling/ Special education/ Mechanical devices/ Orthopedic surgery
- Goal for the treatment program is to maximize function and optimize development in order to help them participate in as many activities as possible in multiple social settings
- Muscle tone management:
 - ✓ Selective dorsal rhizotomy: cutting >50% of the dorsal roots decreases muscle tone in LL
 - ✓ Botulinum toxin: causes presynaptic paralysis of myoneural junctions and reduces abnormal contractions/ Therapeutic effects may last 3-6 months
 - ✓ Intrathecal baclofen infusion: GABA agonist/ baclofen does not cross Blood brain barrier so need high oral doses, lesser dose and lesser SE if given intrathecally
 - ✓ Oral medications:
 - Baclofen (Lioresal): induce hyperpolarization of afferent terminals and inhibit both monosynaptic and polysynaptic reflexes at spinal level
 - Benzodiazepines: potentiate the effects of GABA and facilitate neurotransmission of GABA and other inhibitory transmitters
 - Dantrolene

Complications

Obesity caused by ambulation difficulties/ Constipation/ Gastroesophageal reflux with aspiration pneumonia/ Dental caries/ Aspiration pneumonia/ Bronchial dysplasia/ Asthma/ Decubitus ulcers and skin sores/ Orthopedic contractures, hip dislocations, or scoliosis/ Seizures/ Increased incidence of ADHD , mental retardation, and learning disabilities/ Increased incidence of depression/ Hearing loss ,especially in patients with a history of bilirubin encephalopathy and congenital CMV infection/ Decreased visual acuity, visual field abnormalities , strabismus

Prognosis

- Approximately 25% of patients are unable to walk.
- The ability to sit up by the age of 2 years is a good predictive sign of eventual ambulation
- Children with hemiparesis : walk by 18 m- 36 m.

- With or without assistive devices, 80-90% of children with diplegia, 70% of children with dyskinesia and 50% of children with quadriplegia may achieve some degree of ambulation
- With appropriate therapeutic interventions, many patients may integrate academically and socially
- Although the projected life span of children with CP is less than that of the general population due to complications of motor dysfunction, the majority of affected children will survive well into adulthood if given appropriate medical attention.

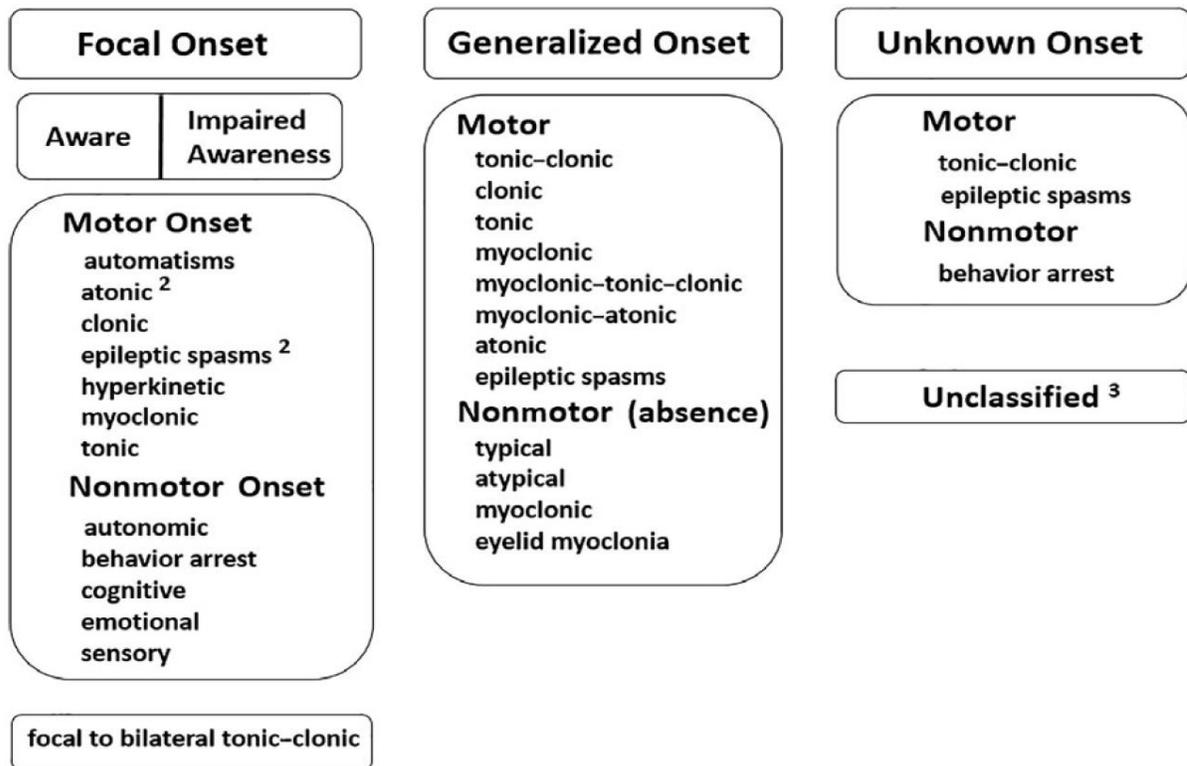
Epilepsy in children

Definitions

- **Seizure:** It is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (cerebrum).
- **Epilepsy:** is a disease of the brain defined by any of the following conditions:
 - ✓ At least two unprovoked (or reflex) seizures occurring more than 24 hours apart.
 - ✓ One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
 - ✓ Diagnosis of an epilepsy syndrome.

Seizure types

ILAE 2017 Classification of Seizure Types Expanded Version ¹



- Atonic seizures and epileptic spasms would not have level of awareness specified
- Cognitive seizures: impaired language/ other cognitive domains/ positive features eg déjà vu, hallucinations, perceptual distortions.
- Emotional seizures: anxiety, fear, joy, etc

- **Simple focal (or partial) seizures** arise from a specific anatomic focus and may or may not spread to surrounding brain regions.
 - ✓ Clinical symptoms include motor (tonic, clonic, myoclonic), sensory, psychic, or autonomic abnormalities.
 - ✓ Consciousness is preserved.
 - ✓ The location and direction of spread of the seizure focus determine the clinical symptoms.
- **Complex partial seizures** can have similar sensorimotor signs
 - ✓ Associated with alteration of consciousness, & (dyscognitive features) may occur.
 - ✓ Patients may have staring and automatisms during complex partial seizures. Automatisms are automatic semi purposeful movements of the mouth (lip smacking, chewing) or extremities (rubbing of fingers). Pedalling is grouped in hyperkinetic rather than automatisms (arbitrary).
- **Focal seizures with secondarily generalized convulsions**
 - ✓ When focal seizures spread to involve the whole brain and produce a generalized seizure, they are said to have secondarily generalized.
 - ✓ Such spread is classically described as progression from face to arm to leg (**Jacksonian march**).
- **Generalized seizures**
 - ✓ Tonic, clonic, and biphasic tonic-clonic seizures may occur alone or in association with other seizure types.
 - ✓ Typically the seizure begins abruptly but occasionally is preceded by a series of myoclonic jerks.
 - ✓ During a tonic-clonic seizure, consciousness and control of posture are lost, followed by tonic stiffening and upward deviation of the eyes.
 - ✓ Pooling of secretions, pupillary dilation, diaphoresis, and HTN are common.
 - ✓ Clonic jerks follow the tonic phase.
 - ✓ In the post-ictal phase, the child might be hypotonic.
 - ✓ Irritability and headache are common as the child awakens.
- **Absence Seizures**
 - ✓ Seizures in which the primary clinical feature is staring can be either absence (generalized) or complex partial seizures.
 - ✓ The clinical hallmark of absence seizures is a brief (less than 15 seconds) loss of environmental awareness accompanied by eye fluttering or simple automatisms, such as fumbling with the fingers and lip smacking.
 - ✓ Absence seizures usually begin between 4 and 6 years of age.
 - ✓ Neurologic examination and brain imaging are normal.

- ✓ The characteristic EEG patterns consist of generalized 3-Hz spike-and-wave activity.
- ✓ A clinical seizure can be provoked by hyperventilation or strobe light stimulation.
- **Atypical absence**
 - ✓ seizures manifest as episodes of impaired consciousness with automatisms, autonomic phenomena, and motor manifestations, such as eye opening, eye deviation, and body stiffening.
 - ✓ They are associated with slower EEG discharges (2 Hz) and other seizure types.
- **Myoclonus**
 - ✓ It is a sudden jerk of all or part of the body; not all myoclonus is epileptic in nature. Nonepileptic myoclonus may be benign, as in sleep myoclonus, or indicate serious disease.
 - ✓ Myoclonic epilepsy usually is associated with multiple seizure types.
 - ✓ The underlying disorder producing myoclonic epilepsy may be static (juvenile myoclonic epilepsy) or progressive and associated with neurologic deterioration (neuronal ceroid lipofuscinosis).
 - ✓ Myoclonic absence refers to the body jerks that commonly accompany absence seizures and atypical absence seizures.
- **Atonic seizures**
 - ✓ Are typically brief (lasting 1 to 2 seconds).
 - ✓ They are quite disabling because of a sudden loss of postural tone, resulting in falls and injuries.
- **Febrile Seizures**
 - ✓ Seizures in the setting of fever may be caused by infections of the nervous system (meningitis, encephalitis, brain abscess), unrecognized epilepsy triggered by fever, or febrile seizures.
 - ✓ Febrile seizure is a seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by an infection of the central nervous system (CNS), without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures
 - ✓ Represents the most common cause of seizures among children between 6 months and 6 years of age.
 - ✓ Occurring in about 4% of all children.
 - ✓ Simple febrile seizures are generalized at onset, last less than 15 minutes and occur only once in a 24-hour period in a neurologically and developmentally normal child.
 - ✓ If there are focal features, the seizure lasts longer than 15 minutes or recurs within 24 hours, or if the child has pre-existing neurologic challenges, the seizure is referred to as a complex or atypical febrile seizure.
 - ✓ The prognosis is excellent.

- ✓ Febrile seizures recur in 30% to 50% of children.
- ✓ The risk of subsequent epilepsy is not substantially greater than that for the general population (approximately 2%).
- ✓ Factors that increase the risk for the development of epilepsy include abnormal neurologic examination or development, family history of epilepsy, and complex febrile seizures.
- ✓ Febrile seizures are brief and the outcome is benign, no treatment is required.
- ✓ Rectal diazepam can be administered during a seizure to abort a prolonged event and is a reasonable option for children with a history of prolonged febrile seizures.
- ✓ Daily administration of anticonvulsant medication is not recommended.
- ✓ Administration of antipyretics during febrile illnesses does not prevent febrile seizures.

Epilepsy syndromes

The epilepsy syndromes represent clinical entities in which age, pattern of clinical events, EEG features, natural history, and prognosis are distinctive.

Neonatal/infantile

- benign familial neonatal epilepsy
 - ✓ An autosomal dominant genetic disorder linked to abnormal neuronal potassium channels.
 - ✓ Response to treatment is generally excellent, and the long-term outcome is typically favourable.
- early myoclonic encephalopathy
- Ohtahara syndrome
- Dravet syndrome
- Myoclonic epilepsy of infancy
- **West syndrome**
 - ✓ It is the triad of infantile spasms, developmental regression, and a dramatically abnormal EEG pattern (hypsarrhythmia).
 - ✓ Hypsarrhythmia consists of chaotic high-voltage slow waves, spikes, and polyspikes.
 - ✓ **Infantile spasms** are brief contractions of the neck, trunk, and arm muscles, followed by a phase of sustained muscle contraction lasting less than 2 seconds. Spasms occur most frequently when the child is awakening from or going to sleep.
 - ✓ The peak age at onset is 3 to 8 months.
 - ✓ Treatment: ACTH, high-dose oral corticosteroids, and vigabatrin (sabril).

childhood

- Panayiotopoulos syndrome
- Epilepsy with myoclonic atonic (previously astatic) seizures
- **Benign Rolandic epilepsy**
 - ✓ Benign epilepsy with centrotemporal spikes
 - ✓ is among the most common epilepsy syndromes
 - ✓ Between ages 5 and 10 years.
 - ✓ The seizures typically occur only during sleep or on awakening in more than half of patients.
 - ✓ Affected children usually have focal motor seizures involving the face and arm (abnormal movement or sensation around the face and mouth, drooling, rhythmic guttural sound).
 - ✓ Speech and swallowing may be impaired. Seizures sometimes secondarily generalize.
 - ✓ The interictal EEG -independent bilateral centrotemporal sharp waves but is otherwise normal.
 - ✓ With a classic history and EEG, and a normal neurological examination, the diagnosis can be made.
 - ✓ Seizures usually respond promptly to anticonvulsant therapy.
 - ✓ Intellectual outcome is normal, and the epilepsy resolves after puberty.
 - ✓ Comorbid learning difficulties and attention deficit/hyperactivity disorder (ADHD) are common.
- Autosomal-dominant nocturnal frontal lobe epilepsy
- Epilepsy with myoclonic absences
- **Lennox-Gastaut syndrome**
 - ✓ usually doesn't respond to antiepileptics
 - ✓ severe epilepsy syndrome with variable age of onset.
 - ✓ Most children present before age 5 years.
 - ✓ Frequent, multiple seizure types, including atonic, focal, atypical absence, and generalized tonic, clonic, or tonic-clonic varieties, characterize the disorder.
 - ✓ Many children have underlying brain injury or malformations.
 - ✓ Most patients have significant intellectual disability.

Adolescent/adult

- juvenile absence epilepsy
 - ✓ Absence seizures typically begin in the early school years and usually resolve by late childhood or adolescence.

- ✓ If absence does not remit, 44% will go on to develop juvenile myoclonic epilepsy.
- ✓ Ethosuximide is the first-choice therapy.
- ✓ A subset of patients also has generalized tonic-clonic seizures. For these children, valproic acid is the first choice as it can prevent both absence and convulsive seizures.
- juvenile myoclonic epilepsy
 - ✓ Onset is typically in early adolescence with myoclonic jerks (**exacerbated in the morning, often causing the patient to drop objects**), generalized tonic-clonic seizures, and absence seizures.
 - ✓ medication (classically valproic acid) must be maintained for life.
- epilepsy with generalized tonic-clonic seizures alone
- progressive myoclonus epilepsies
- autosomal dominant epilepsy with auditory features

Variable age

- Familial focal epilepsy with variable foci
- reflex epilepsies

Acquired epileptic aphasia (Landau-Kleffner syndrome)

- Characterized by the abrupt loss of previously acquired language in young children.
- The language disability is an acquired cortical auditory deficit (auditory agnosia).
- The EEG is highly epileptiform in sleep, the peak area of abnormality often being in the dominant perisylvian region (language areas).
- Young patients with clear autistic regression.
- Potentially treatable entity.

Etiology

- Symptomatic (the cause is known): structural (Vascular, trauma, tumor, cortical, hypoxic ischemic), infectious, metabolic (GLUT1 deficiency), immune (Rasmussen syndrome)
- Idiopathic, Genetic (Trisomies, angelman, klinefelter)
- Cryptogenic (probably there is an underlying cause but it is not evident at the moment)

Treatment

- 1st seizure: don't treat
- Modalities of treatment:
 - ✓ Antiepileptic drug therapy (more details in the next sheet)
 - Generalized epilepsy: valproic acid (depakin, convulex)
 - Partial epilepsy: carbamazepine (tegretol)

- DRUGS THAT AFFECT VOLTAGE-DEPENDENT SODIUM CHANNELS
 - Old : Carbamazepine Phenytoin
 - New : Lamotrigine, Oxcarbazepine, Zonisamide, Lacosamide, Rufinamide
- DRUGS THAT AFFECT CALCIUM CURRENTS
 - Ethosuximide
- DRUGS THAT AFFECT GABA ACTIVITY
 - Benzodiazepines, barbiturates, gabapentine
- DRUGS THAT AFFECT GLUTAMATE RECEPTERS
 - topiramate
- DRUGS WITH MULTIPLE MECHANISMS OF ACTION
 - Topiramate, valproic acid
- Unknown
 - Levetiracetam
- ✓ Immune therapy (rasmussen)
- ✓ Treatable metabolic disorders (pyridoxine, folonic acid)
- ✓ Ketogenic diet
 - High fat (80%), low carbs, adequate protein
 - If seizure free, diet discontinued
- ✓ Atkins diet (under investigation)
- ✓ Epilepsy surgery
 - If focal area of ictal onset can be identified
 - Lesionectomy/ lobectomy/ corpuscallosotomy/ hemispherectomy/ multilobar resection
- ✓ Vagal nerve stimulation
 - Pacemaker behind left carotid
- ✓ Deep brain stem stimulation (under investigation)

Prognosis

- 50% will outgrow their epilepsy and stop treatment
- Stop treatment if free of seizure for 2 years

Sources: nelson essentials/ slides from Dr. Abdelkarim Alqudah & Dr. Amira Almasri

Esraa Alkubaisi & Rafeef Qawasmeh

Antiepileptic Drugs

Drug	Use	Side effects
Carbamazepine <i>Tegretol</i>	Partial seizure Trigeminal neuralgia 2 nd bipolar disorder	- <i>Hyponatremia (SIADH)</i> -sedation -rash (characteristic) -leucopenia *increasing the dose should be gradual to avoid harmful side effects
Valproic acid <i>Depakin , convulex</i>	Broad spectrum AED Used for generalized tonic-clonic seizure	-tremor -confusion - weight gain 90% , weight loss 10% -elevated liver enzymes -hepatic enzyme inhibitor - teratogenic neural tube defects - polycystic ovary So its best for males not for females ! Increase the dose gradually to avoid toxicity
Lamotrigine Lamictal	Used as an add on therapy	-rash increasing the dose should be every 2 wks. -tremor -headache -allergic: Esinophilia Steven Johnson Lymphadenopathy Arthralgia safest drug in pregnancy drug of choice for females > 12 years
Topiramate Topamax		-kidney stones -weight loss -gluacoma -acidosis -fever
Zonisamide		-kidney stones -fever
Felbamate		-aplastic anemia

		-hepatic toxicity , not used except in Lennox Gastaut.
Gabapentine Neurontin		Aggression and hyperexcitability
Ethosoxamide Zarontin	Absence seizure	
Vigabatrin sabril + ACTH	West syndrome	
Phenytoin & Phenobarbital	Used for emergencies	<p>Pheytoin: Megaloblastic anemia , decreased folic acid , teratogenicity , nystagmus, gingival hypertrophy , drug induced lupus.</p> <p>Clinical pearls : -what is the drug of choice for neonatal seizure? Phenobarbital</p> <p>-patient with head injury + seizure , what is the drug of choice ? Phenytoin , unlike phenobarbital , it <i>doesn't</i> affect the level of consciousness. So to monitor LOC in patient with head injury use phenytoin.</p> <p>-<u>status epilepticus</u> patient must be monitor for : 1. Blood pressure: hypotension may be caused by side effects of some drugs . so its very important to keep monitoring the blood pressure. 2. Cardiac function: arrhythmia can be a side effect of phenytoin.</p>

As a general rule:

Generalized seizure : valproic acid

Partial seizure: carbamazepine

Broad spectrum AEDs are:

valproic acid

lamotrigine

topiramate

Slow titration:

Lamotrigine

Topiramate

Zonisamide

-carbamazepine **worsens** absence , atonic and myoclonic seizures.

The End.

Ala'a Abu-Shattal

2014-2015

Status Epilepticus in children: update



Amira Masri

Professor of pediatric neurology
Faculty of Medicine –The University of Jordan

Definition



- Conventional “textbook” definition of status epilepticus:
 - Single seizure > 30 minutes
 - Series of seizures > 30 minutes without full recovery

Why 30 min ???



Animal experiments in the 1970s and 1980s had shown that ...

... neuronal injury could be demonstrated after 30 min of seizure activity, even while maintaining respiration and circulation

Nevander G. Ann Neurol 1985;18(3):281-90



More practical definition

- shortening the required seizure duration from 30 min to 5 min
- Impending or early stage of SE (5-30 min)
- Established state of SE (30-60 min)

Why ??????



- Seizures that do not cease in 5-10min are less likely to terminate without intervention

Eriksson K et al. Neurology 2005; 65:1316.

Chin RF et al. Lancet Neurol 2008; 7:696.



The longer SE persists,

- the lower is the likelihood of spontaneous cessation
- the harder it is to control
- the higher is the risk of morbidity and mortality

Bleck TP. *Epilepsia* 1999;40(1):S64-6

The Status Epilepticus Working Party. *Arch Dis Child* 2000;83(5):415-9.



New definitions

- **Impending status epilepticus** “an acute epileptic condition characterized by continuous generalized convulsive seizures for at least 5 minutes or by continuous non-convulsive seizures or focal seizures for at least 15 minutes, or by two seizures without full recovery of consciousness between them”
- **Established status epilepticus** :“an acute epileptic condition characterized by continuous seizures for at least 30 minutes, or by 30 minutes of intermittent seizures without full recovery of consciousness between the seizures”



Refractory status epilepticus

- Clinical or EEG seizure lasting longer than 60 minutes despite treatment with at least 1 first-line AED (ie, benzodiazepine) and 1 second-line AED (ie, phenytoin, phenobarbital, or valproate).
- 25% - 50% of children in case series of SE

Sahin M, et al *Epilepsia* 2001;42:1461–7. Koul R et al. *J Child Neurol* 2002;17:908–10. Lambrechtsen FA et al *Epilepsia* 2008;49:615–25



Why do seizures evolve into status ??

- Super-refractory status epilepticus : status that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases that recur on the reduction or withdrawal of anaesthesia.
- 15% of all the cases with status epilepticus admitted to hospital will become super-refractory

Shorvon and Trinka, 2011, Shorvon S, Ferlisi M. *Brain*. 2011 Oct;134(Pt 10):2802-18



- Failure of the normal mechanisms that *limit* the spread and recurrence of isolated seizures

Excessive Excitation

Ineffective inhibition

- Multiple mechanisms probably are involved.

Lowenstein DH et al .*N Engl J Med* 1998; 338:970.
Hanhan UA et al *Pediatr Clin North Am* 2001; 48:683



Epidemiology of SE in children

- incidence in children :17 - 23 episodes per 100,000 per year
- Incidence rates, causes, and prognosis vary substantially by age.

Chin RF et al. Lancet 2006; 368:222. Raspall-Chaure M et al. Epilepsia 2007; 48:1652.



- Highest incidence : in the first year of life.
- Febrile status epilepticus is the most common etiology
- 60 %of children are neurologically healthy prior to the first episode of SE.

Singh et al.Neurology 2010; 74:636.



Risk factors for SE

- Epilepsy : 10 – 20% of children with epilepsy will have at least one episode of SE
- SE as the first seizure : 12% of children with epilepsy.
- partial seizures in clusters (three or more within 24 hours) :higher incidence of SE

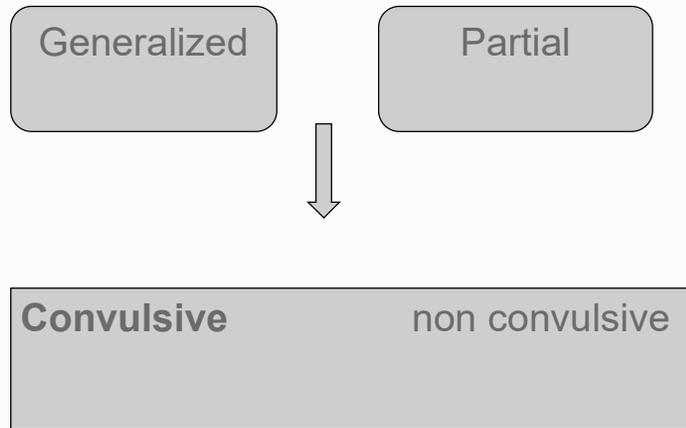
Shinnar Set al. Pediatrics 1996; 98:216. Haut SRet al. Epilepsia 1999; 40:1832.



- History of prior SE
- Young age <1 yr at onset
- Symptomatic etiology of epilepsy
- Genetic factors
- Genetic syndromes (Dravet syndrome, generalized epilepsy with febrile seizures plus or GEFS+, Angelman syndrome)



Classification: Seizure Types



Etiologies

- Fever =most common 36%
- Medication change 20%
- Unknown 9%
- Metabolic 8%
- Congenital 7%
- Anoxic 5%
- Other (trauma, vascular, infection, tumor, drugs) 15%



FEVER-INDUCED REFRACTORY EPILEPTIC ENCEPHALOPATHY AND FIRES

- School-aged children
- Febrile infection-related epilepsy
- Cause ?
- Refractory seizures
- Poor prognosis
- First line and second line drugs , anesthetic agents , Immunomodulatoryttt : not effective
- ketogenic diet: reported to be effective in few cases

Brain Dev 2009;31:92–3., Kramer U et al. Epilepsia 2011;52:1956–65. , Howell KB, et al. Epilepsia 2012;53:101–10.

Nabbout R, et al Epilepsia 2010;51:2033–7.

Author's personal copy

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Manifestations and treatment of epilepsy in children with neurometabolic disorders: A series from Jordan

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ABSTRACT

Purpose: To examine the characteristics of epilepsy in children with neurometabolic disorders to reveal co morbidities and optimal treatment.

Methods: We retrospectively reviewed the files of children diagnosed with a neurometabolic disorder and treated at Jordan University Hospital between 2001 and 2012. We examined the incidence, age at onset, clinical characteristics, and medical control of epilepsy.

Results: Cases treated (40 boys, 30 girls) included the different categories of neurometabolic diseases. Twenty-nine patients (41.4%) were also diagnosed with epilepsy, with age at seizure onset ranging from 3 days to 7 years. All types of seizures were reported, but generalized tonic-clonic and mixed types were most common (16/29 patients, 55.2%). Patients were on either a single antiepileptic drug (16/29, 55.2%) or multiple drugs (13/29, 44.7%), and most drugs prescribed were older generation anticonvulsants. Complete seizure control was achieved in 19/29 patients (65.5%), partial control in 7/29 (24.1%), and poor or no control in 3/29 (10.3%). EEG recordings were missing from the medical files of 10/29 patients. The first EEG revealed epileptiform activity in 12/19 patients (63.2%) and was normal in 7/19 patients (36.8%).

Conclusions: Epilepsy was diagnosed in about half of pediatric neurometabolic disease patients, with the majority of seizure cases well controlled.

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Original article

Profile of developmental delay in children under five years of age in a highly consanguineous community: A hospital-based study – Jordan

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Abstract

Aim: To assess etiologies and risk factors for global developmental delay (GDD) in children.

Patients and methods: Between January 2006 and 2007, a retrospective study was carried out at the Child Neurology Clinic of Jordan University Hospital on all 229 children under five years of age presenting with GDD. To assess risk factors for GDD, 229 age-matched healthy children were included as controls.

Results: A definite etiology for GDD could be determined in 103 (44.5%) patients, while 127 (55.5%) patients remained undiagnosed. The most common category for the GDD was cerebral palsy (CP) seen in 72 patients (31.4%), of which the underlying etiology was determined in 50 patients (69.5%). The second most common category was metabolic disorders where a definite metabolic cause was reached in 15 (6.5%) patients and a possible metabolic cause was suspected in 16 (6.9%) cases. Other etiologies included other monogenic disorders in 12 (5.2%) patients, brain malformations in 7 (3.0%) patients, chromosomal abnormalities in 6 (2.6%) patients, and autism in 12 (5.2%) patients. History of perinatal complications and consanguinity were major risk factors ($p < 0.05$).

Conclusion: To our knowledge this is the first and largest study on GDD in a highly consanguineous Arab population. Cerebral palsy and metabolic disorders were the most common causes of GDD in Jordan, while perinatal complications and consanguinity were the major risk factors contributing to GDD.

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Systemic complications

- Metabolic: lactic acidosis
- Hypoxia
- Aspiration pneumonia, pneumonitis
- Hyperpyrexia
- Glucose alteration
- Blood pressure disturbances
- Arrhythmia
- High Output CHF (rare)
- High WBC
- Increased ICP

Outcome :mortality

- Mortality=3-15% in children
- The primary determinant of mortality and morbidity of SE in children is its etiology
- Greatest mortality +morbidity : occurs when SE is caused by an acute neurological condition (infection, trauma, stroke)
- Kravljanac R et al. Epilepsia 2011; 52:358.

Temporary systemic changes

Life threatening systemic changes

Death

Duration of seizure



Outcome :morbidity

- Morbidity other than epilepsy : 15 %of patients
- Neurologic sequelae are usually caused by the underlying condition rather than the seizures

[Kravljianac Ret al. Epilepsia 2011; 52:358.](#)



- A** Oxygen, oral airway. Suction. Avoid hypoxia!
- B** Consider bag-valve mask ventilation. Consider intubation
- C** IV/IO access. Treat hypotension, but NOT hypertension



Treatment

General Measures

Stabilization

Brief history and examination



Initial investigations

- Labs
 - Na, Ca, Mg, PO₄ , glucose
 - CBC
 - Liver function tests, ammonia
 - Anticonvulsant drug level
 - Toxicology

in presence of hypoglycemia; seizure will not abort until you give glucose.
so lab investigations are important

385



Initial investigations

- Lumbar puncture: if indicated
 - defer LP in unstable patients
 - never delay antibiotic/antiviral treatment if indicated



Neuroimaging : indications

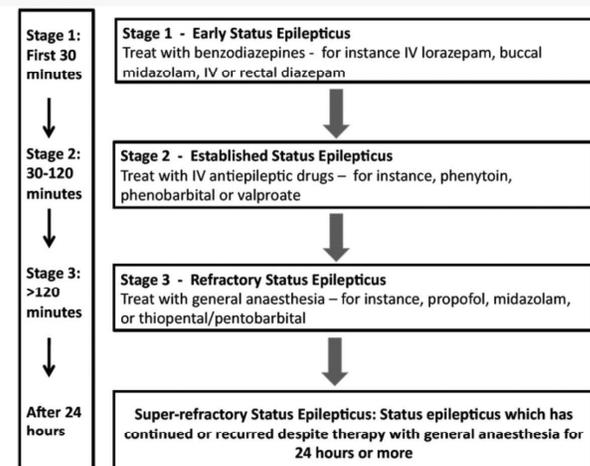
- When status epilepticus is the first presentation of epilepsy
- Focal seizures
- Focal deficit or focal EEG
- History of trauma or bleeding disorder
- Children whose recovery from SE does not follow the expected course

Singh RK et al. Neurology 2010; 74:636. , Yoong M et al. Dev Med Child Neurol 2012; 54:328.



Treatment in children

- Many protocols
- Comparative data : limited
- Approaches have not been validated by clinical trials
- Protocols : should be adapted to what is there in your hospital



Appleton R. Arch Dis Child 2000; 83:415 Appleton R. et al. Arch Dis Child 2000; 83:415.



Anticonvulsants

Rapid acting

plus

Long acting

- Give appropriate doses



Anticonvulsants - Rapid acting

- Benzodiazepines
 - **Lorazepam**(iv, rectal, sublingual,im)
0.1 mg/kg i.v. over 1-2 minutes
 - **Diazepam**(iv, rectal)
0.1-0.3 mg/kg i.v. over 1-2 minutes
Diazepam 0.2-0.5 mg/kg rectal
If SE persists, repeat every 5-10 minutes(max 3 doses ,10mg)
 - **Midazolam**: iv, buccal, nasal,im
– 0.15-0.3mg/Kg IV



Benzodiazepines

- **Lorazepam** less side effects
 - Low lipid solubility
 - Action delayed 2 minutes
 - Anticonvulsant effect 6-12 hrs
 - Less respiratory depression than diazepam
- **Diazepam**
 - High lipid solubility
 - Thus very rapid onset (10-20 sec)
 - Redistributes rapidly
 - Thus rapid loss of anticonvulsant effect(20min)
 - Adverse effects are persistent:
 - Hypotension
 - Respiratory depression

Appleton R et al. Dev Med Child Neurol 1995; 37:682.
Chiulli Daet al J Emerg Med 1991; 9:13.



If no IV access

- Intramuscular midazolam
- Intramuscular lorazepam

Chamberlain JM. Pediatr Emerg Care 1997;13(2):92-4.
Towne AR. J Emerg Med 1999;17(2):323-8.



Anticonvulsants - Long acting

Phenytoin

corrosive to vessels

- Extravasation causes severe tissue injury
- Onset 10-30 min
- May cause hypotension, dysrhythmia
- not given IM, given slowly
- Cheap

Fosphenytoin

Extravasation well tolerated

- Onset 5-10 min
- May cause hypotension
- IV administration associated with burning and nonallergic pruritis, usually in the **perineal** area
- Expensive
- less arrhythmia
- prophenytoin



Anticonvulsants - Long acting

- Phenobarbital
 - 15-20 mg/kg i.v. over 15 - 30 min
 - Onset 15-30 min
 - May cause hypotension, respiratory depression



If SE continues

- Valproic acid loading 10-15mg/kg iv
- Paraldehyde loading 150-200mg/kg iv slowly over 15-20 min (9min glass not plastic)



Valproic acid

- Don't need to place patient on monitor
- Very few side effects even at high doses
- Effective in 78-100% of children with refractory status



Vitamin B6

- Children <3 years



If SE persists=ICU , ventilation ,
continuous EEG monitor

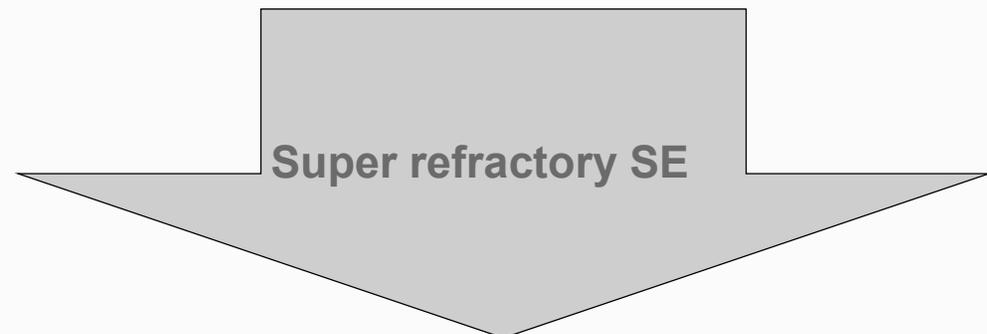
- Propofol
- Midazolam
- Pentobarbital
- Thiopental
- Isoflurane , halothene



- Conventional choice :thiopental (or pentobarbital), propofol and midazolam.
- Each has advantages and drawbacks
- No controlled or randomized comparative data on which to base a choice



- Other drugs





not at emergency room **Topiramate**

- Case series (pt were also on other medical measures)
- slow titration :control in 3-6 days
- Higher dose :response within 1 day without any noted side effects.

Not useful in initial status epilepticus
Useful add-on medication after patients have been treated with coma induction.

Kahrman M et al. Epilepsia 2003; 44:1353., Blumkin L et al. J Child Neurol 2005; 20:239. , Perry M et al Epilepsia 2006; 47:1070.



Levetiracetam

- Oral and intravenous preparations
- The intravenous form is not approved for use in children.
- Limited published data in children

Abend Ns et al Pediatr Neurol 2008; 38:377. , Reiter Pdet al Pediatr Neurol 2010; 43:117. , Gallentine W et alv. Epilepsy Behav 2009; 14:215.



ketogenic diet

- Case reports in children :usefulness in super refractory status and in FIRES
- Mech ?anti-inflammatory effect
- Should not be used with propofol :Propofol infusion syndrome

Pediatr Neurol. 2014 Jan;50(1):101-3, J Child Neurol. 2014 Jan 23
François et al., 2003, Nabbout et al. (2010)



Corticosteroids, Adrenocorticotrophic Hormone, IVIG , Plasmapheresis

- Few case reports
- Autoimmune etiologies :Rasmussen's encephalitis / vasculitis.
- Many cryptogenic cases might be due to occult immunological diseases with antibodies that have yet to be identified.



Other effects of steroids

- Reversal of blood–brain barrier opening
- Effects on intracranial pressure.

Brain. 2011 Oct;134(Pt 10):2802-18.



Electroconvulsive Therapy

- Enhance –aminobutyric acid transmission
- Few studies : reported efficacy in adults and children

Seizure. 2012 Nov;21(9):661-4,Seizure. 2011 Jun;20(5):433-6.



Hypothermia

- Few data regarding efficacy or safety in epilepsy or status epilepticus.

Further studies are necessary

Epilepsia. 2013 Sep;54(9):1586-94



Surgery

- If a focal area of ictal onset can be identified.
- Often widespread epileptogenic areas : poor outcome after surgery .

Vagal nerve stimulation



- Four published cases (children):benefit from VNS
- In all these cases: extensive additional therapy complicating the assessment of the effect of VNS

Winston et al., 2001; Herdt et al., 2009
Patwardhan et al., 2008; O'Neil et al., 2011

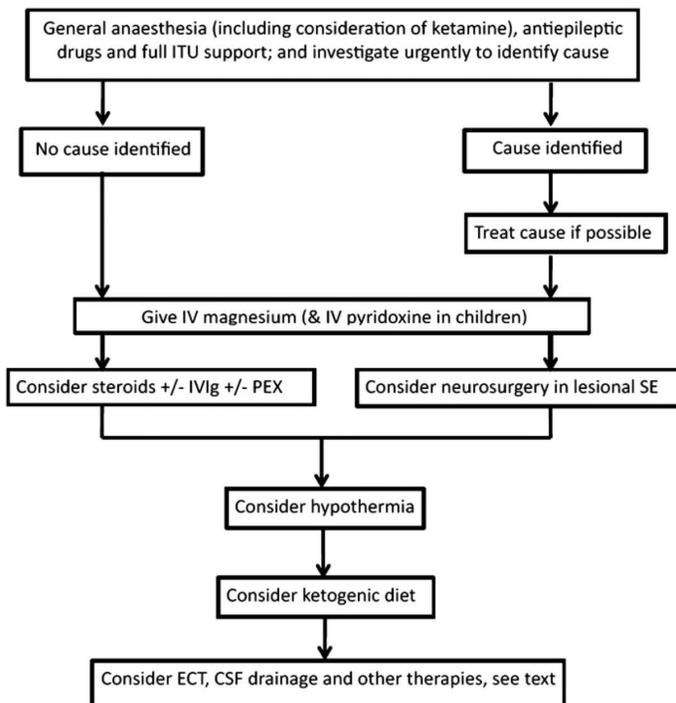


Others

- CSF drainage
- Deep brain stem stimulation



Limited data



Titration Goals and Duration



coma-inducing agents :

- unclear whether the treatment goal should be termination of seizures, burst suppression, or a complete suppression of electroencephalogram activity.
- unclear for how much the patient should be in coma



- Further research is needed in children
- Most protocols suggest maintaining a coma for 24-48 hours



- Study of 22 children with refractory status epilepticus:
- All survivors manifested intractable epilepsy
- Suggests that a continuation of high-dose suppressive therapy because of some seizures during the weaning phase may not improve the likelihood of a seizure-free outcome.
- Further studies are needed to elucidate the optimal weaning parameters



Weaning of Coma-Inducing Medications

- Few data regarding the optimal rate of weaning, or the amount of seizure burden or number and types of epileptiform discharges that can be tolerated.
- Many seizures may occur during weaning from coma-inducing medications, and may be solely electrographic.

Nicholas S. Abend *Pediatr Neurol.* 2008 Jun;38(6):377-90



Conclusions

- Current thinking : the emergency treatment of SE should be faster and more aggressive.
- It is associated with the progressive, time-dependent development of pharmacoresistance.
- Many unresolved issues
- Further studies (multicenter) are needed

Neonatal seizure

The occurrence of neonatal seizures may be the first, and perhaps the only, clinical sign of a central nervous system (CNS) disorder in the newborn infant.

Neonatal seizures are abnormal electrical discharges in the CNS of neonates and usually manifest as stereotyped muscular activity or autonomic changes (alterations in heart rate, respiration and blood pressure, flushing, salivation, and pupil dilatation). There are sensory manifestations but a preverbal infant cannot communicate sensory phenomena associated with seizures.

Most neonatal seizures are focal, probably because generalization of electrical activity is impeded in neonates by lack of myelination and incomplete formation of dendrites and synapses in the brain.

Classification of seizures (according to motor manifestations):

- **Focal clonic** — repetitive, rhythmic contractions of specific muscle groups of the limbs, face, or trunk. Clonic movements typically have a slow rate of repetition, particularly when larger muscle groups are involved. Cannot be suppressed by restraint.
- **Multifocal clonic**
- **Focal tonic** – sustained, but transient, asymmetrical posturing of the trunk or extremities or tonic deviation of the eyes. Cannot be provoked by stimulation or suppressed by restraint.
- **Generalized tonic**
- **Myoclonic** – arrhythmic contractions of muscle groups of the limbs, face, or trunk. Typically not repetitive or may recur at a slow rate. May be provoked by stimulation. divided into focal, multifocal, and generalized.
- **Subtle seizures** – include transient eye deviations, nystagmus, blinking, mouthing, abnormal extremity movements, fluctuations in heart rate, hypertension episodes, and apnea. Subtle seizures occur more commonly in premature than in full-term infants.
- **Spasms** are sudden generalized jerks lasting 1-2 sec
- **Subclinical seizures**

Etiology

Ages 1-4 days	Ages 4-14 days	Ages 2 – 8 weeks
<ul style="list-style-type: none"> • Hypoxic-ischemic encephalopathy • Drug withdrawal, maternal drug use of narcotic or barbiturates • Drug toxicity: lidocaine, penicillin • Intraventricular hemorrhage • Acute metabolic disorders • Inborn errors of metabolism • Pyridoxine deficiency (must be considered at any age) 	<ul style="list-style-type: none"> • Infection • Metabolic disorders • Drug withdrawal, maternal drug use of narcotics or barbiturates • Benign neonatal convulsions, familial and nonfamilial • Kernicterus, hyperbilirubinemia 	<ul style="list-style-type: none"> • Infection • Head injury • Inherited disorders of metabolism • Malformations of cortical development • Lissencephaly • Tuberos sclerosis

- **Hypoxic ischemic encephalopathy** (postasphyxial seizures) – the most common cause. They frequently present within the first 72 hours of life.
- **Intracranial hemorrhage** – including subarachnoid, intracerebral, and intraventricular hemorrhage, may cause seizures. Intraventricular hemorrhage, which occurs more commonly in premature infants, results from bleeding in the germinal matrix. Seizures with IVH are associated with a bulging fontanelle, hemorrhagic spinal fluid, anemia, lethargy, and coma.
- **Congenital brain malformations**
- **infarctions**
- **Neonatal infections** – such as meningitis and sepsis. Encephalitis due to CMV, HSV, rubella virus, *Treponema pallidum*, or *Toxoplasma gondii* can also cause seizures.
- **Metabolic disturbances** – hypoglycemia, hypo- or hypernatremia, hypocalcemia and hypomagnesemia.
- **Inborn errors of metabolism** – Non-ketotic hyperglycinemia, D-glycemic acidemia, Methylmalonic acidemia. Rarely, pyridoxine deficiency or dependency causes seizures.
- **Maternal substance abuse** – (eg, cocaine, heroin, diazepam) is an increasingly common problem; seizures can accompany acute withdrawal after birth.

- **Benign neonatal seizure syndromes** – can be characterized by familial or idiopathic seizures.
 - **Benign idiopathic neonatal seizures** – or benign neonatal convulsions typically present at day 5 of life (ie, fifth day fits). No specific etiology although several hypotheses have been investigated acute zinc deficiency in CSF and rotavirus in stool of affected infants. Seizures occur within the first seven days of life, with 90 percent occurring between days four and six, and they resolve within two weeks. No family history of seizures, and normal neurologic examinations between seizures.
 - **Benign familial neonatal seizures** – typically occur in the first 48-72 hours of life; the seizures disappear by age 2-6 months. A family history of seizures is usual. Development is typically normal in these infants. Characterized as a channelopathy, caused in most cases by mutations in voltage-gated potassium channel genes (*KCNQ2* and *KCNQ3*). The disorder is inherited in an AD pattern.
- **Severe neonatal epileptical syndromes** – should be suspected in newborns who lack an obvious cause for acute symptomatic seizures. They are often associated with refractory seizures and poor neurodevelopmental outcomes – Early myoclonic encephalopathy (EME), early infantile epileptic encephalopathy (EIEE), *KCNQ2* encephalopathy and DEND syndrome (Developmental delay, Epilepsy, and Neonatal Diabetes) due to mutations in the *KCNJ11* gene.

Differential diagnosis

- Seizures may be difficult to differentiate from benign jitteriness or from tremulousness in infants of diabetic mothers, in infants with narcotic withdrawal syndrome, and in any infants after an episode of asphyxia.
- **Jitteriness** must be differentiated from seizures in neonates. Jitteriness is not associated with ocular deviation. It is stimulus sensitive (eg, triggered by stimulation or easily stopped with passive movement of the limb). The movement resembles a tremor, and no autonomic changes, such as tachycardia, are associated with it.
- **Benign sleep myoclonus** – The clinician should be familiar with this benign condition, in which rhythmic movements (which occur only during sleep) mimic seizures. The condition can be alarming and may occur focally during nonrapid eye movement (non-REM) sleep. Video EEG monitoring shows no electrographic seizures.

Diagnostic evaluation

- Taking the prenatal and postnatal history and performing an adequate physical examination.
- Laboratory tests – to look for underlying treatable causes
 - Serum glucose and electrolytes – sodium, calcium, magnesium. (not potassium).
 - TORCH infection studies.
 - Urine organic acids.
 - Serum amino acid assay.
 - Renal function tests - These tests rule out posthypoxic renal dysfunction.
 - CSF analysis.
- EEG – plays a vital role in properly identifying and differentiating neonatal seizures from nonepileptic events. Bedside EEG with video monitoring for ≥ 24 h may detect ongoing clinically silent electrical seizures, particularly in the first few days after a CNS insult.
- Imaging studies – do MRI at 7-10 days of age. Brain CT not done.

Treatment

- **ABC**
- **Treatment of the cause:**
 - Hypoglycemia – 10% dextrose 2 mL/kg IV is given, and the serum glucose level is monitored; additional infusions are given as needed but cautiously, to avoid hyperglycemia.
 - Hypocalcemia – 10% calcium gluconate 1 mL/kg IV (9 mg/kg of elemental calcium) is given; this dosage can be repeated for persistent hypocalcemic seizures. Rate of calcium gluconate infusion should not exceed 0.5 mL/min (50 mg/min). Extravasation should be avoided because skin may slough.
 - Hypomagnesemia – 0.2 mL/kg (100 mg/kg) of a 50% magnesium sulfate solution is given IM.
 - Bacterial infections are treated with antibiotics.
 - Herpes encephalitis is treated with acyclovir.
- **Anticonvulsants** - Anticonvulsants are used unless seizures stop quickly after correction of reversible disorders.
 - Phenobarbital is the initial drug of choice. If seizures persist, the use of phenytoin should be considered.
 - **Phenobarbital** – a loading dose of 15 to 20 mg/kg IV is given. If seizures continue, 5 to 10 mg/kg IV can be given q 15 to 30 min until seizures cease or until a maximum of 40 mg/kg is given.

- **Levetiracetam** is being increasingly used to treat neonatal seizures because it is less sedating than phenobarbital.
- **Fosphenytoin** can be used if seizures continue despite phenobarbital and levetiracetam. The loading dose is 20 mg PE (phenytoin equivalents)/kg IV. It is given over 30 min to avoid hypotension or arrhythmias.
- **Lorazepam** 0.1 mg/kg IV may be used initially for a prolonged seizure or for resistant seizures and repeated at 5- to 10-min intervals, up to 3 doses in any 8-h period.
- **Don't treat with diazepam**, as it can cause respiratory depression and jaundice.

Prognosis

- Prognosis of neonatal seizures has become better owing to improvement and advancement of obstetric care and intensive neonatal care.
- Mortality from neonatal seizures has decreased from 40 to 20%.
- EEG is highly associated with the outcome in premature and full-term infants. predictors of less-favorable later outcome:
 - abnormal background is a powerful.
 - prolonged electrographic seizures (>10 min/hour)
 - multifocal periodic electrographic discharges
- spread of the electrographic seizures to the contralateral
- The underlying etiology of the seizures is the main determinant of outcome.

Sources: merckmanuals, UpToDate, Medscape, nelson essentials, Dr. Abdelkarim AlQudah slides and Dr. Eman Badran notes

Rafeef Al-Qawasmeh

Epilepsy imitators

Definitions

- Range of conditions associated with recurrent paroxysmal events that may imitate and be misdiagnosed as epilepsies.
- Several conditions can result in abnormal movements, sensations, or loss of awareness, but may not be associated with an abnormal electrical discharge in the brain.

Syncope and anoxic seizures

- Vasovagal syncope
 - ✓ affects all ages
 - ✓ brief, lasting seconds
 - ✓ Preceded by triggers
 - ✓ Convulsive movements occur in 50 %
 - ✓ Positive F. Hx is common
- Reflex anoxic seizures
 - ✓ Occurs from early infancy onwards, either remit or evolve into vasovagal
 - ✓ Preceded by sudden stimulus such as bump or knock, result in profound vagal stimulus, transient asystole
 - ✓ Child become exceedingly pale and loss of consciousness, tonic posturing in possible
- Breath-holding attacks
 - ✓ affect pre-school children
 - ✓ Start with crying then stop breathing in expiration
 - ✓ becomes blue with deep cyanosis
 - ✓ They breath in or go to transient syncope, tonic posturing in possible
 - ✓ more common if the child has iron deficiency anemia
- Hyperventilation syncope
- Compulsive valsalva
- Neurological syncope
- Imposed upper airways obstruction
- Orthostatic intolerance
- Long QT and cardiac syncope
 - ✓ In long QT syndrome a ventricular tachyarrhythmia may be spontaneous or triggered by fright, exercise, surprise, and immersion in water.
 - ✓ Syncope in sleep, a strong family history of syncope and a history of sudden death or drowning should raise suspicions of a cardiac syncope.

- ✓ Sensorineural deafness is associated with some types of long QT syndrome
- Hyper-cyanotic spells

Behavioral, psychological, and psychiatric disorders

- Daydreaming /inattention
- Infantile gratification
 - ✓ self-stimulation includes behavior which may be seen from infancy onwards, more so in pre-school girls.
 - ✓ Rhythmic hip flexion and adduction may be accompanied by a distant expression, a flushed face and sometimes followed by sleepiness.
- Eidetic imagery
- Tantrums and rage reactions
 - ✓ Temper tantrums can be defined as episodes of extreme frustration and anger that manifest in an array of signs ranging from whining, screaming, stomping, hitting, head banging, and falling to more severe actions such as breath holding, vomiting, and aggression, including biting. The child often appears to be “out of control.”
 - ✓ Tantrums occur equally in boys and girls during the preschool period.
 - ✓ Temper tantrums are considered part of typical behavior in 1- to 4-year-old children.
- Out of body experiences
- Panic attacks
- Dissociative states
- Non-epileptic seizures
- Hallucinations in psychiatric disorders
- Fabricated / factitious illness

Sleep related conditions

- Sleep related rhythmic movement disorders
- Hypnagogic jerks
- Parasomnias
 - ✓ sleep disorders that occur during the first 1/3 of night sleep (in non-REM phase) and involve unwanted behavior and movements. These occur most commonly at the age of 4–12 years.
 - ✓ Stress, restlessness, and infections are thought to be triggering factors.
 - ✓ Confusional arousal, night terrors, and sleepwalking are the most common parasomnias in childhood

- REM sleep disorders
 - ✓ characterized by sleep-related motor and behavioral changes including laughing, speaking, groaning, and kicking during REM phase.
- Benign neonatal sleep myoclonus
 - ✓ It is characterized by repetitive, high-frequency myoclonic jerks in the arms and legs, which last for seconds or minutes, especially while falling asleep following feeding in the neonatal period.
 - ✓ If the child wakes up, the episode is over; the most important feature is that it is not observed outside of sleep.
 - ✓ These episodes usually disappear spontaneously when the child is 4–6 months old.
- Periodic leg movements
- Narcolepsy-cataplexy

Paroxysmal movement disorders

- Tics
 - ✓ involuntary, sudden, rapid, repetitive, non-rhythmic, simple or complex movements or vocalizations
 - ✓ common in childhood and have a tendency to wax and wane in frequency over time
 - ✓ urge or compulsion to perform the tic, and an ability to suppress the tic (to some degree) are important features on history that support the diagnosis
- Stereotypies
 - ✓ Stereotypes are recurrent, simple movement groups that can be stopped voluntarily. They most commonly occur as recurrent movements in patients with mental retardation and autism.
 - ✓ They are usually concentrated in the upper extremities and do not occur in the lower extremities.
 - ✓ They markedly increase during periods of stress.
 - ✓ They can be stopped with initiation of another activity or distraction of the child.
- Paroxysmal kinesigenic dyskinesia
- Paroxysmal nonkinesigenic dyskinesia
- Paroxysmal exercise induced dyskinesia
- Benign paroxysmal tonic upgaze
 - ✓ It consists of a clinical picture of chronic and recurrent ataxia associated with upward deviation of the eyes with a constant or variable period. The clinical picture of ataxia may not be noticed in all patients.
 - ✓ The attacks last for a short period.

- ✓ The age of onset ranges between 1 month and 2 years. In children with a normal neurologic development, it is expected to recover spontaneously in 1–2 years from onset.
- Episodic ataxias
- Alternating hemiplegia
- Hyperekplexia
 - ✓ characterised by an exaggeration of the normal startle response and has several genetic linked to dysfunction of the inhibitory glycinergic pathway in the nervous system
 - ✓ evident from the neonatal period or early infancy
 - ✓ Die of apnea
- Opsoclonus-myoclonus syndrome
 - ✓ autoimmune neurological disorder that may be seen in association with neuroblastoma, following viral infections...
 - ✓ The earliest feature is often ataxia followed by opsoclonus, followed by myoclonus

Episodic syndromes that may be associated with migraine

- Recurrent gastrointestinal disturbance
 - ✓ Cyclical vomiting syndrome
 - Recurrent episodic attacks of intense nausea and vomiting, usually stereotypical in the individual and with predictable timing of episodes.
 - Attacks may be associated with pallor and lethargy.
 - There is complete resolution of symptoms between attacks.
 - Boys and girls are equally,
 - The usual age of onset is 5 years
 - Typically a self-limiting episodic condition occurring in childhood, children will “outgrow” these attacks by age 10
 - ✓ Abdominal migraine
- Benign paroxysmal vertigo
 - ✓ recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, after minutes to hours without loss of consciousness, in otherwise healthy children,
 - ✓ Associated with at least one of the following: nystagmus, ataxia, vomiting, pallor, fearfulness
- Benign paroxysmal torticollis

- ✓ Recurrent episodes of head tilt to one side, perhaps with slight rotation, which remit spontaneously. The condition occurs in infants and small children, with onset in the first year.
- ✓ Associated with at least one of the following: pallor, irritability, malaise, vomiting, ataxia

Miscellaneous events

- Benign myoclonus of infancy and shuddering attacks
 - ✓ Shuddering attack is an NEPE that initiates with rapid tremor of the head and shapes with continuance of this movement in the shoulder and trunk. The attacks last only for 1–2 seconds and they are benign movements that recur frequently (sometimes 100 times a day). Nursing, eating, and urination may initiate the attacks. They occur at the age of 4–6 months and disappear spontaneously at the age of 6–8 years. Treatment is unnecessary.
- Jitteriness
 - ✓ It is the most common movement disorder in the neonatal period. The most important features that differentiate this movement, which is composed of recurrent tremors in the extremities, include increase of movement with stimuli and stopping of the movement with slight flexion of the extremity. Eye movements and autonomic changes (hypertension, apnea) do not occur; presence of these changes suggests epileptic episodes. It may be physiologic (benign) or may occur pathologically as a result of hypoglycemia, hypocalcemia, hypoxic ischemic encephalopathy, intracranial hemorrhage, sepsis, hypothermia, hyperthyroidism and drug withdrawal reactions.
- Sandifer syndrome
 - ✓ This syndrome is seen in young children with gastro-oesophageal reflux (with or without vomiting).
 - ✓ Events are often seen with or after feeding. Typically there is arching of the back, dystonic posturing of the limbs and turning/tilting of the head.
- Non-epileptic head drops
- Spasmus nutans
- Paroxysmal extreme pain disorder
- Spinal myoclonus

Sources: Slides from Dr. Abdelkarim Alqudah, Nelson essentials,
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5509124/>

Autism Spectrum Disorder

Autism was first described in 1943 by Kanner, and by 1980 it was officially recognized as a diagnosis in DSM-III

DEFINITION

It is a biologically based neurodevelopmental disorder, characterized by impairments in two major domains:

- deficits in social communication and social interaction
- restricted repetitive patterns of behavior, interests, and activities

Autism spectrum disorder (ASD) encompasses disorders previously known as autistic disorder (previous DSM-IV):

- classic autism
- childhood disintegrative disorder
- pervasive developmental disorder-not otherwise specified
- Asperger disorder

EPIDEMIOLOGY

- The prevalence of ASD increased over the last decades (maybe due to changes in case definition or increased awareness of autism. Whether or not the actual incidence of autism has increased is unclear)
- It's a common disorder affecting 1:50-500 children, with male predominance (M:F is 4:1)
- 15-20% of cases of autism are pure autism. The rest are with mental retardation & different neurological disorders

TERMINOLOGY

- DSM-5 criteria for autism:
 - persistent deficits in social communication and interaction (eg, deficits in social reciprocity; nonverbal communicative behaviors; and skills in developing, maintaining, and understanding relationships)
 - restricted, repetitive patterns of behavior, interests, or activities

The symptoms must be present in early development, but may not become manifest until social demands exceed limited capacities thus precluding the previous criteria of symptoms before a specified age cutoff.

Comparison of changes in the DSM-IV & DSM-V for ASD	
DSM-IV	DSM-V
Rett disorder	Rett disorder is eliminated because it's considered a genetic disease
pervasive developmental disorder-not otherwise specified, Asperger disorder, childhood disintegrative disorder	These three disorders will now officially be called ASD
Unusual sensory behaviors not part of the criteria	Unusual sensory behaviors will be added to the criteria
3-symptom categories (impairment in social interaction, impairment in communication, and repetitive and restrictive behaviors)	2-symptom categories (deficits in social communication and social interaction combined, and repetitive and restrictive behaviors) but more criteria required per category.

- (ICD-10) classifies autism spectrum disorder as “pervasive developmental disorders” and includes several subtypes, including childhood autism, atypical autism, and Asperger syndrome, among others.

PATHOPHYSIOLOGY

- Pathophysiology is unknown.
- Hypothesis:
 - ✓ Abnormalities of cellular configurations in several regions of the brain, including the frontal +temporal lobes and the cerebellum.
 - ✓ Elevations of whole blood serotonin occur in one third of patients.
 - ✓ Elevated levels of C-terminally directed betaendorphin protein immunoreactivity.
"The basis and importance of these findings is unknown"
 - ✓ Impairment in the metabolism of phenolic amines:
 - Symptoms of autistic disorder, therefore, are possibly aggravated by the consumption of dairy products, chocolates, corn, sugar, apples, and bananas, but there are no large population studies for confirmation.
 - ✓ The role of obstetric complications is unclear.
 - ✓ Genetic and environmental factors:
 - Likely have an equal effect on determining an autism diagnosis, sibling risk rates >25%.
 - ✓ Immunizations & Folic acid consumption in pregnancy = no association and are not risk factors

DIAGNOSIS

Often diagnosis is delayed, Early identification and intervention improves the outcome.

CLINICAL PICTURE

Usually starts at 9-10 months, Some remain normal until 18-24 months of age then lose social and language milestones:

- ✓ Decrease crying , feeding , motor activity
- ✓ Delayed language development
- ✓ No appropriate response to noises (axaggerated or decreased)
- ✓ Fascinated with a particular toy
- ✓ Stereotypic behavior or gesture:
 - flapping the hands and arms
 - Head banging rhythmic movements
 - rocking from the pelvis
- ✓ Better verbal than non-verbal skills
- ✓ Echolalia (meaningless repetition of another person's spoken words)
- ✓ Expressive and comprehensive problems

NOTE : Motor milestones are often normal

HISTORY

- absence of protodeclarative pointing:
 - protodeclarative pointing is the use of the index finger to indicate an item of interest to another person, its absence is predictive of the later diagnosis of autism.
 - Screening questions include:
 - ✓ "Does your child ever use his/her index finger to point, to indicate interest in something?"

The absence of a positive response to this question suggests the need for a specialized assessment for possible pervasive developmental disorder.
- Unusual responses to environmental stimuli :
 - Parents report unusual responses to environmental stimuli, including excessive reaction or an unexpected lack of reaction to sensory input.
 - Children with autistic disorder may also display exaggerated responses or rage to everyday sensory stimuli,such as bright lights.
- Social interactions:
 - Separation from parents may elicit a lack of appropriate eye contact
 - Absence of typical responses to pain and physical injury: Rather than crying and running to a parent when cut or bruised, the child may display no change in behavior.
 - Difficulties in social interactions are common.
 - Problems making friends
 - show attachments to objects not normally predicted to be child oriented
 - Speech abnormalities are common (speech delay was the most common cause for presentation to the clinic in a study that was conducted in Jordan, while 0% of parents presented to the clinic worried about social delay only, although social delay and speech delay present in the same percent of autistic children).
 - language delays and deviations.
 - Pronominal reversals are common, including saying "you" instead of "I."

- Playing :
 - Absence of symbolic play in infants and toddlers is highly predictive of the later diagnosis of autism.
 - Odd play : interest in parts of objects instead of functional uses of the whole object.
 - Examples of play :
 - ✓ Spinning a wheel of a car
 - ✓ Enjoy repeatedly lining up or dropping objects from a particular height.
 - ✓ fascinated with items that are not typical toys, such as pieces of string.
 - ✓ They may spend hours watching traffic lights, fans, and running water.
- Self-injurious behaviors (in minority of patients):
 - Skin picking
 - Self biting
 - Head punching and slapping
 - Head-to-object and body-to object banging; body punching and slapping
 - Poking the eye, the anus, and other body parts
 - Lip chewing; removal of hair and nails; and teeth banging.

PHYSICAL EXAMINATION

- Head features:
 - Head circumference is elevated
 - Aberrant palmar creases and other dermatoglyphic anomalies
 - Look for hints for certain syndromes that can manifest as autism

EARLY DETECTION

- Developmental surveillance should be performed at all well-child visits:
 - ✓ Developmental screening tests should be administered regularly at the 9-, 18-, and 24- or 30-month visits, and when developmental concerns are raised.
 - ✓ Further developmental evaluation is required whenever a child fails to meet any of the following milestones:
 - ☒ Babbling by 12 months
 - ☒ Gesturing (e.g., pointing, waving bye-bye) by 12 months
 - ☒ Single words by 16 months
 - ☒ Two-word spontaneous (not just echolalic) phrases by 24 months
 - ☒ Loss of any language or social skills at any age.
- All children should be screened for autism at 18 and 24 months.

Screening tools for Autism Spectrum Disorder			
Measure	Acronym	Age range	Description
Infant and toddler checklist (also called :Communication and Symbolic Behavior Scales and Developmental Profile)	ITC CSBS-DP	9- 24 months	Designed to screen for communication delays but recently has tested well for early autism screening
Modified Checklist for Autism in Toddlers	M-CHAT	16- 30 months	23-item yes/no questionnaire
Childhood Autism Screening Test	CAST	4-11 years	Has some research toward use as a universal screening device

- Siblings of children with autism should be carefully monitored

DIAGNOSTIC TESTS

- Measures relying on parent report :
 - ✓ The Autism Behavior Checklist (ABC)
 - ✓ Gilliam Autism Rating Scale, 2nd edition (GARS-2)
 - ✓ the Autism Diagnostic Interview-Revised (ADIR).
- Measures using direct observation :
 - ✓ The Childhood Autism Rating Scale (CARS)
 - ✓ the Autism Diagnostic Observation Schedule-Generic (ADOS-2).

DIAGNOSIS

Diagnosis is made clinically according to DSM-V criteria. child will need to meet the criteria in A, B, C,D, and E:

- A → Persistent deficits in social communication and social interaction across multiple contexts, Examples :
 - ✓ Deficits in social-emotional reciprocity; ranging, for example, from abnormal social approach and failure of normal back and forth conversation; to reduced sharing of interests, emotions, or affect, to failure to respond to social interactions.
 - ✓ Deficits in nonverbal communicative behaviors used for social interaction; ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expression and nonverbal communication.
 - ✓ Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends;to absence of interest in peers.
- B → Restricted, repetitive patterns of behavior, interests,or activities as manifested by at least two of the following:
 - ✓ Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping object, echolalia, idiosyncratic phrases).

- ✓ Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
 - ✓ Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
 - ✓ Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of environment (e.g. apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
- C→ Symptoms must be present in the early developmental period but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life.
 - D→ Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
 - E → These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

NOTE

- ☒ Individuals with a well-established **DSM-IV** diagnosis of autistic disorder, Asperger’s disorder, or pervasive developmental disorder not otherwise specified, should be given the diagnosis of autism spectrum disorder.
- ☒ Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Table 1. **Severity Levels for Autism Spectrum Disorder**

Severity Level	Social Communication	Restricted, repetitive behaviors
Level 3: Requiring very substantial support	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches.	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2: Requiring substantial support	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication.	Inflexibility of behavior, difficulty coping with change, or other restricted/ repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1: Requiring support	Without supports in place, deficits in social communication cause noticeable social impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful.	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

DIAGNOSE THE ETIOLOGY

- good history and examination : orient dx +investigations
- Only in < 10% of cases we find an etiology
- Syndromes associated with Autism:
 - ✓ Tuberous sclerosis complex:
 - ☒ 17 – 60% of patients with tuberous sclerosis complex also have ASD
 - ☒ Only 0.4 – 4% of patients with ASD have tuberous sclerosis
 - ✓ Fragile X :
 - ☒ 30 – 50% of patients with fragile X syndrome have features of ASD
 - ☒ fragile X syndrome is rarely found in patients with autism
 - ✓ 15q chromosome duplications/triplications
 - ✓ PKU
 - ✓ Down syndrome
 - ✓ Angelman syndrome (15q deletions)
 - ✓ Rett syndrome.
 - ✓ Smith-Lemli-Opitz syndrome
 - ✓ Various metabolic conditions including:
 - ☒ mitochondrial abnormalities
 - ☒ cerebral folate deficiency
 - ☒ disorders of creatine transport or metabolism
 - ☒ sulfation defects
 - ✓ Others – Other chromosomal "hot spots" include chromosome 1, 2, 3q, 5p, 7q,11q, 12q, 13q, 16p, 17, 18q, 21p, 22q, and X

Table 3. **Syndromes Associated With Autism^a**

Autism-Related Syndrome	Physical Examination and/or History Findings	Associated Gene(s)	Patients With Syndrome Who Have Autism, %	Patients With Autism Who Have Syndrome, %	Testing to Consider
Tuberous sclerosis	Ash leaf spots, adenoma sebaceum, shagreen patches, tubers, seizures, and intellectual disability	<i>TSC1</i> and <i>TSC2</i>	20–40	1	MRI, ophthalmology, cardiac and renal evaluation
Neurofibromatosis	2 criteria of the following: 6 café au lait spots, ≥2 neurofibromas or 1 plexiform, axillary or inguinal freckling, optic glioma, ≥2 Lisch nodules, sphenoid dysplasia or tibial pseudoarthrosis, first-degree relative with neurofibroma type 1	<i>NF1</i>	40–50 in some studies	0.3	Ophthalmology consultation, MRI, spinal examination for scoliosis, cardiac for murmurs, and blood pressure for hypertension
Angelman syndrome	Language and Intellectual deficits, seizures, hypermotoric and ataxic movements, paroxysms of laughter, and happy disposition	<i>UBE3A</i>	50	Rare	FISH or microarray testing for 15q11.2–q13, EEG, MRI
Fragile X syndrome	Inconsistent physical examination findings, microcephaly and macrocephaly, large jaw, large hands, macro-orchidism	<i>FMR1</i>	25 (males) and 6 (females)	1–2	Fragile X testing looking for CGG repeats >200
Rett syndrome	Regression in development, hand-wringing behavior, female, microcephaly	<i>MECP2</i>	All females, but with DSMV will be considered separate disorder	Rare	EEG, <i>MECP2</i> gene testing

INVESTIGATIONS

- ✓ Metabolic screen for PKU
- ✓ Chromosomal microarray and for fragile X
- ✓ Hearing test
- ✓ Lead (only if history is suggestive)
- ✓ EEG (only if seizure)
- ✓ MRI isn't routinely indicated

CO-OCCURRING DIAGNOSES

- ✓ Intellectual disability :in 50% of cases
- ✓ Medical problems:sleep disorders, constipation, and irritability
- ✓ Anxiety and phobia
- ✓ ADHD
- ✓ disruptive behaviors
- ✓ Obsessive compulsive disorder
- ✓ Depression
- ✓ Bipolar disorders
- ✓ EEG abnormalities and seizures :20-25%

TREATMENT

There's no cure for autism, and there's no "one-size-fits-all" treatment. It needs prolonged and skilled effort:

- ✓ Behavioral and communication therapies:
 - General goals:
 - ☒ Maximize functioning
 - ☒ Move the child toward independence
 - ☒ Improve the quality of life for the child and family
 - Specific goals:
 - ☒ Improve social functioning and play skills
 - ☒ Improve communication skills (both functional and spontaneous)
 - ☒ Improve adaptive skills
 - ☒ Decrease nonfunctional or negative behaviors
 - ☒ Promote academic functioning and cognition
 - Core features of successful autism educational programs:
 - ☒ A high staff-to-student ratio (1:1 or 1:2)
 - ☒ Individualized programming for each child
 - ☒ Teachers with special expertise in working with children with autism
 - ☒ A minimum of 25 hours per week of services
 - ☒ Ongoing program evaluation and adjustment
 - ☒ A curriculum emphasizing attention, imitation, communication, play, and social interaction
 - ☒ A highly supportive teaching environment
 - ☒ Predictability and structure
 - ☒ Functional analysis of behavior problems
 - ☒ Transition planning

- ☒ Family involvement
- ✓ Drug therapies:
 - Right now, there are no medications that seem to directly improve the core signs of autism. Medications are used to treat targeted symptoms (Hyperactivity, inattention, and impulsivity, Aggression, outbursts, and self-injury, Anxiety, Obsessive compulsive behaviors, rigidity, repetitive behaviors, depressive symptoms & sleep dysfunction):
 - Atypical antipsychotics :
 - ☒ risperidone : reduces serious behavioral (problems like temper tantrums , aggression ,self injury)
 - ☒ olanzapine
 - Mood stabilizers :
 - ☒ divalproex sodium
 - ☒ levetirecetam
 - ☒ lithium
 - Selective serotonin reuptake inhibitors

Selected pharmacotherapeutic agents used for symptom management in children and adolescents with autism spectrum disorders

Agent	Targeted symptom(s)	Potential adverse effects
Atypical antipsychotic agents (eg, risperidone*, anipiprazole*, olanzapine)	Aggression Hyperactivity/inattention Repetitive behavior Sleep disturbance	Weight gain Metabolic syndrome Tremor Extrapyramidal symptoms Increased salivation Sedation
Stimulants (eg, methylphenidate, dextroamphetamine, dexmethylphenidate)	Hyperactivity/inattention/impulsivity	Decreased appetite Difficulty falling asleep Irritability Social withdrawal
Selective serotonin reuptake inhibitors (eg, fluoxetine, fluvoxamine, sertraline, paroxetine, etc)	Aggression Anxiety Depression Repetitive behavior	Potential increased risk of suicidal ideation Behavioral activation Irritability
Alpha-2-adrenergic agonists (eg, guanfacine, clonidine)	Aggression Hyperactivity/inattention Sleep disturbance	Sedation Fatigue Irritability Constipation Hypotension Rebound hypertension if discontinued abruptly
Anticonvulsant mood stabilizers (eg, valproic acid)	Aggression Hyperactivity/inattention Repetitive behaviors Sleep disturbance	Mood lability Fatigue Insomnia Diarrhea Weight gain Increased appetite
Atomoxetine	Hyperactivity/inattention	Potential increased risk of suicidal ideation Irritability Gastrointestinal symptoms Fatigue
Melatonin	Sleep disturbance	Difficulty waking Daytime sleepiness Enuresis
Mood stabilizer (eg, lithium)	Aggression	Weight gain Nausea Frequent urination

- ✓ Complementary and alternative therapies
 - Lack of evidence
 - Some cause harm

PROGNOSIS

- Continue to develop albeit at a slower rate than expected and do not deteriorate
 - IQ is highly correlated with the prognosis:
 - ❖ Low-functioning patients :
 - ☒ never live independently(need home or residential care for the rest of their lives)
 - ❖ High-functioning patients:
 - ☒ live independently,hold jobs successfully, and even marry and have children.
- "High-functioning individuals with autistic disorder are similar to people with Asperger syndrome"

Factors that have been associated with positive outcomes	Factors associated with less favorable outcomes
Presence of joint attention	Lack of joint attention by four years of age
Functional play skills	Lack of functional speech by five years of age
Higher cognitive abilities	IQ <70
Decreased severity of autism symptoms	Severe autism symptoms
Early identification	Seizures or other comorbid medical or neurodevelopmental conditions
Involvement in intervention	
A move toward inclusion with typical peers	

Source: slides by Dr.Amira
Organized by: Raya Al-Majali

Attention Deficit Hyperactivity Disorder

DEFINITION

Attention deficit hyperactivity disorder (ADHD) is a childhood onset neurodevelopmental disorder that often continuing into adulthood. it's characterized by developmentally inappropriate and impairing inattention, motor hyperactivity, and impulsivity.

Primary symptoms include :

- ✓ Inattention or distractibility:
Visual, auditory, "thought"-daydreaming
- ✓ +/- Impulsiveness :
'must be first', 'just do it'
- ✓ +/- Hyperactivity:
Fidgety, restless, talkative

EPIDEMIOLOGY

- Prevalence in school-age children :8-10%
- More common in boys :
M:F ratio→
 - ✓ 4:1 for the predominantly hyperactive type
 - ✓ 2:1 for the predominantly inattentive type
- No evidence of rise in rates of symptoms or diagnosis of ADHD across time

PATHOPHYSIOLOGY

Pathogenesis is not definitively known:

- Genetic imbalance of catecholamine metabolism in the cerebral cortex appears to play a primary role:
 - ✓ Genetic → number of genes identified that appear to play a role
 - ✓ Catecholamine metabolism→ increase in dopamine transporter density may clear dopamine from the synapse too quickly
 - ✓ Neuroanatomy and functional brain imaging findings:
 - Reversed or absent asymmetry of the caudate nucleus
 - Smaller cerebral and cerebellar volume
 - Smaller posterior corpus callosum regions
 - Increased gray matter in the posterior temporal and inferior parietal cortices
 - Smaller prefrontal cortical volumes
 - Reduced thickness of the anterior cingulate cortex
 - Cortical thinning in bilateral superior frontal brain regions

- Reduced global activation
 - Reduced local activation in the area of the basal ganglia and anterior frontal lobe
- Various environmental factors may play a secondary role. Its significance is controversial. Potential environmental influences include:
 - Dietary factors :
 - food additives, sugar, food sensitivity, essential fatty acid deficiency, mineral deficiency
 - generally do not impact behavior to a clinically significant level and do not account for the majority of cases of ADHD.
 - However, a small subset of children may demonstrate mild adverse behavioral effects in response to dietary influences.
 - Prenatal exposure to tobacco.
 - Other factors that have been associated with the development of ADHD, but in which the association is inconsistent, include :
 - ✓ prematurity and low birth weight
 - ✓ prenatal exposure to alcohol
 - ✓ head trauma.

DIAGNOSIS

There's no biological or anatomical marker, diagnosis is made clinically:

	Inattentive symptoms	Hyperactivity or impulsivity symptoms
1	Doesn't give close attention to details or makes careless mistakes	Fidgets with or taps hands or feet, or squirms in seat
2	Has difficulty sustaining attention on tasks or play activities	Leaves seat in situations when staying seated is expected
3	Doesn't seem to listen when directly spoken to	Runs about or climbs when not appropriate (may present as feelings of restlessness in adolescents or adults)
4	Doesn't follow through on instructions and doesn't finish schoolwork, chores, or duties in the workplace	Unable to play or undertake leisure activities quietly
5	Has trouble organizing tasks or activities	"on the go", acting as if "driven by a motor"
6	Avoids , dislikes ,or is reluctant to do tasks that need sustained mental effort	Talks excessively
7	Loses things needed for tasks or activities	Blurts out answers before a question has been finished
8	Easily distracted	Has difficulty waiting his or her turn
9	Forgetful in daily activities	Interrupts or intrudes on others

DSM-5 diagnostic criteria for ADHD:

- if <17 years →
 - ✓ ≥6 symptoms of hyperactivity and impulsivity OR ≥6 symptoms of inattention.
- If ≥17 years →
 - ✓ ≥5 symptoms of hyperactivity and impulsivity OR ≥5 symptoms of inattention are required.
- The symptoms of hyperactivity/impulsivity or inattention must be :
 - ✓ Be present in more than one setting (eg, school and home)
 - ✓ Persist for at least six months
 - ✓ Be present **before** the age of 12 years
 - ✓ Impair function in academic, social, or occupational activities
 - ✓ Be excessive for the developmental level of the child
- other physical, situational, or mental health conditions that could account for the symptoms must be excluded.

NOTE : ICD-10 in Europe has a more restrictive criteria than DSM-5 . it Requires that at least six symptoms of inattention, at least three symptoms of hyperactivity, and at least one symptom of impulsivity are present in more than one setting.

Other common presentations for ADHD:

- Preschool years :
 - ✓ Motor restlessness (always on the go)
 - ✓ Aggressive (hits others)
 - ✓ Spills things
 - ✓ Insatiable curiosity
 - ✓ "Fearless—may endanger self or others
 - ✓ Low levels of compliance
 - ✓ Vigorous and often destructive play
 - ✓ Demanding, argumentative, noisy
 - ✓ Interrupts others
 - ✓ Excessive temper tantrums
- School children :
 - ✓ Easily distracted
 - ✓ Homework poorly organized, careless errors, often incomplete or lost
 - ✓ Low academic scores
 - ✓ Frequent trips to the principal's office
 - ✓ Blurts out answers before question completed (often disruptive in class)
 - ✓ Often interrupts and intrudes on others

- ✓ Low self-esteem
- ✓ Displays aggression
- ✓ Difficult peer relationships
- ✓ Does not wait turns in games
- ✓ Often out seat
- ✓ Perception of “immaturity”
- ✓ Unwilling or unable to do chores at home
- ✓ Accident prone
- Adolescents :
 - ✓ May have sense of inner restlessness rather than hyperactivity
 - ✓ Procrastinates and displays disorganized school work with poor follow-through
 - ✓ Fails to work independently
 - ✓ Poor self-esteem
 - ✓ Poor peer relationships
 - ✓ Inability to delay gratification
 - ✓ Specific learning disabilities
 - ✓ Behavior not usually modified by reward or punishment
 - ✓ Engages in “risky” behavior (speeding, unprotected sex, substance abuse)
 - ✓ Apparent disregard for own safety (injuries and accidents)
 - ✓ Difficulties or clashes with authority

NOTE: The response to stimulant medication cannot be used to confirm or refute the diagnosis of ADHD. Stimulant medications improve behavior in children with ADHD & in children with conditions other than ADHD (eg, learning disabilities, depression), and in normal control children.

CLINICAL SUBTYPES

- **Predominantly inattentive:**
 - ✓ Easily distracted, Not excessively hyperactive or impulsive in behavior
 - ✓ Symptoms may not appear until 8-9 years
 - ✓ Symptoms may persist throughout life
 - ✓ 20-30% of patients
- **Predominantly hyperactive-impulsive**
 - ✓ Extremely hyperactive and impulsive, Not highly inattentive (may have no inattentive signs)
 - ✓ Often younger children
 - ✓ After 7-8 years symptoms of hyperactivity begin to decline. In adolescents it's barely observed (may feel restless)
 - ✓ <15% of patients

- **Combined type:**
 - ✓ All three classical signs of the disorder
 - ✓ Most patients 50-75%

CO-MORBIDITIES

- ✓ Oppositional defiant disorder (ODD) → 50-80%
- ✓ Conduct disorder (risk marker for greater neurocognitive impairment and worse prognosis) → one third
- ✓ Depression → one third
- ✓ Anxiety disorder → 20-40%
- ✓ learning disabilities → 20-60%

EVALUATION

- Medical evaluation :
 - ✓ Obtain detailed clinical history from parents or carers and young person
 - ✓ Carry out core ADHD symptom enquiry: are symptoms out of keeping with child's age and developmental stage ?
 - ✓ Obtain information across settings ; consider questionnaires as an adjunct
 - ✓ Screen for associated difficulties (e.g. mental health symptoms , other neurodevelopmental or learning problems)
 - ✓ Complete history :
 - Developmental history (eg. Motor delay)
 - Medical history (e.g. epilepsy)
 - Family history (e.g. mental health, educational history , physical health problems)
 - Medical histories especially important in relation to cardiac or other risk factors if pharmacological treatment is being considered
 - ✓ Consider severity of symptoms , effects on functioning, comorbid symptoms , medical history , and the family and child's strengths , resources , demands , and psychosocial context when deciding on treatment options.
 - ✓ Physical assessment :
 - Signs of other disorders (e.g. dysmorphic features , skin lesions) and motor coordination (e.g. handwriting, balance) ; to be undertaken more completely if considering pharmacological treatment
 - Baseline height , weight , blood pressure , pulse .

- Developmental and behavioral evaluation :
 - ✓ Behavior rating scales:
 - **ADHD-specific scales:**
 - Also called narrow-band scales
 - Focus directly on the symptoms of ADHD
 - Sensitivity and specificity >90% :
 - ❖ Vanderbilt Assessment Scales → children \geq 4yrs
 - ❖ Conners Comprehensive Behavior Rating Scales → includes preschool
 - ❖ ADHD Rating Scale IV → includes preschool
 - **Broadband scales**
 - Assess a variety of behavioral symptoms, including, but not limited to, the core symptoms of ADHD
 - Less sensitive and specific (< 85%)

Note: recommended to establish the presence of the core symptoms of ADHD help to identify coexisting conditions and narrow the differential

- Educational evaluation
- Evaluation for co-existing disorders

Note : Psychometric testing not indicated as routine. EEG , neuroimaging , genetic tests ,lead , ferritin etc ...: not necessary in the evaluation (unless indicated by the clinical evaluation).

Ratings scales in the assessment and monitoring of ADHD

Scales	Behaviors assessed
Broadband assessment	
Conners 3 rd Edition ^[1]	Inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, peer relations, DSM-IV symptoms scales for inattentive, hyperactive-impulsive and combined type of ADHD (DSM-5 scoring is also available as a Supplement), ODD, conduct disorder
Behavior Assessment System for Children (BASC) ^[2]	Hyperactivity, aggression, conduct problems, anxiety, depression, somatization, atypicality, withdrawal, attention problems, learning problems, lack of adaptability/social/leadership/study skills
Child Behavior Checklist/Teacher Report Form ^[3,4]	Somatic complaints, social/thought/attention problems, anxiety/depression, aggressive/delinquent behavior, withdrawal
Narrow-band assessment	
ADHD Comprehensive Teacher's Rating Scale (ACTeRS): Boys' and girls' form ^[5]	Attention problems, hyperactivity, lack of social skills, oppositional
ADHD Rating Scale ^[6]	Symptoms of ADHD according to DSM-IV criteria
Childhood Attention Problems Scale ^[7]	Combined measure of attention problems, impulsivity, hyperactivity
Conners 3 rd Edition: Short version ^[1]	Selected items from the long version to measure inattention, hyperactivity/impulsivity, learning problems, executive function, aggression, and peer relations
BASC Monitor Rating Scale ^[8]	Attention/adaptive problems, hyperactivity, problems with internalizing
Disruptive Behavior Rating Scale ^[9]	DSM-IV symptoms of ODD, ADHD, and CD (parent form only)
Vanderbilt Assessment Scales ^[10,11]	Symptoms of ADHD according to DSM-IV criteria; screen for comorbid conditions (ODD, CD, anxiety, depression)
Assessment of medication side effects	
Side Effects Rating Scale ^[9]	Sleeping/appetite problems, staring/daydreaming, withdrawal, anxiety, irritability, somatic complaints, emotional lability, dizziness, tics

Emotional and behavioral disorders that commonly coexist with attention deficit hyperactivity disorder in children and adolescents

Disorder	Clinical features
Conduct disorder	Repetitive and persistent violation of age-appropriate societal norms, rules, or basic rights of others; includes: <ul style="list-style-type: none"> • Aggression to people and animals • Destruction of property • Deceitfulness or theft • Serious violations of rules
Anxiety disorder	Persistent, excessive, difficult to control worry about events or activities; associated with: <ul style="list-style-type: none"> • Restlessness • Easy fatigability • Difficulty concentrating • Irritability • Muscle tension • Sleep disturbance
Depression	Persistent disturbance in emotions, ideation, or somatic symptoms as indicated by ≥ 5 of the following symptoms; at least one of the symptoms in red must be present: <ul style="list-style-type: none"> • Depressed or irritable mood • Markedly diminished interest or pleasure in almost all activities • Change in appetite or weight • Insomnia or hypersomnia • Psychomotor agitation or retardation • Fatigue or loss of energy • Feelings of worthlessness or guilt • Impaired concentration, indecisiveness • Recurring thoughts of death or suicide
Learning disability	Intrinsic cognitive difficulty that results in lower academic achievement than expected for intellectual potential; examples include: <ul style="list-style-type: none"> • Reading disorder • Disorder of written language • Mathematics disorder • Learning disorder, not otherwise specified
Oppositional defiant disorder	Recurrent negative, defiant, disobedient, and hostile behavior toward authority figures, including: <ul style="list-style-type: none"> • Losing temper • Arguing with adults • Actively defying or refusing to comply with adults' requests or rules • Deliberately annoying people • Blaming others for his or her mistakes or misbehavior • Being touchy or easily annoyed by others • Being angry and resentful • Being spiteful or vindictive

DIFFERENTIAL DIAGNOSIS

Symptoms of ADHD overlap with other conditions:

- ✓ developmental variations
- ✓ neurologic or developmental conditions
- ✓ emotional and behavioral disorders
- ✓ psychosocial or environmental factors

NOTE: Some of these conditions can coexist with ADHD and may or may not be responsible for some of the symptoms. These conditions can be differentiated from ADHD with a thorough history and/or the use of a broadband behavior rating scale.

Differential diagnosis for attention-deficit hyperactivity disorder in children and adolescents*

	Methods to distinguish from ADHD
Developmental variations	
Intellectual disability	Psychometric testing
Giftedness	Psychometric testing
Normal variation	History
Neurologic or developmental disorders	
Learning disability	Psychometric testing
Language or communication disorder	Psychometric testing
Autism spectrum disorders	History; structured observation
Neurodevelopmental syndromes (eg, fetal alcohol syndrome, fragile X syndrome)	History; examination; genetic testing
Seizure disorder	History; electroencephalography if clinically indicated
Sequelae of central nervous system trauma or infection	History
Motor coordination disorder	History; examination; occupational therapy evaluation
Emotional/behavioral disorders	
Depression or mood disorder	Broadband behavior scale; mental health evaluation
Anxiety disorder	Broadband behavior scale; mental health evaluation
Oppositional defiant disorder	Broadband behavior scale; mental health evaluation
Conduct disorder	Broadband behavior scale; mental health evaluation
Obsessive compulsive disorder	Broadband behavior scale; mental health evaluation
Post-traumatic stress disorder	Broadband behavior scale; mental health evaluation
Adjustment disorder	Broadband behavior scale; mental health evaluation
Psychosocial or environmental problems	
Child abuse or neglect	Medical history; psychosocial history; examination
Stressful home environment	Psychosocial history
Inadequate or punitive parenting	Psychosocial history
Parental psychopathology or substance abuse	Psychosocial history
Inappropriate educational setting	Symptoms occur at school but not at home
Frequent school absence	Psychosocial history
Selected medical conditions	
Hearing or vision impairment	Hearing and vision screen
Sleep disorder	History; sleep study as indicated by clinical findings
Iron deficiency anemia	Complete blood count and other hematologic studies as indicated
Lead poisoning	Measurement of blood lead level
Endocrine disorders (eg, thyroid disease, diabetes mellitus)	Laboratory studies as indicated by clinical findings
Cardiac disorders (eg, heart failure)	Medical history; echocardiograph/pediatric cardiology consultation as indicated
Substance abuse	History; toxicology screening
Food allergy	History; allergy testing as indicated
Undernutrition	Assessment of growth parameters
Medication side effects	History

TREATMENT

- criteria for initiation of pharmacotherapy in children with ADHD:
 - ✓ diagnostic assessment is complete and confirms diagnosis of ADHD
 - ✓ child is age six years or older (younger than six years should be managed by consultation with a specialist since the effect of stimulants on preschool children is unpredictable)
 - ✓ parents accept medication as contribution to management
 - ✓ school will cooperate in administration and monitoring

- ✓ no previous sensitivity to the chosen medication
- ✓ child has normal heart rate and blood pressure
- ✓ child is seizure free
- ✓ child doesn't have Tourette syndrome
- ✓ child doesn't have pervasive developmental delay
- ✓ child doesn't have significant anxiety
- ✓ substance abuse among household members isn't a concern (for children who will be treated with immediate release stimulants)
- medications :
 - stimulants (1st line)→
 - Methylphenidate :
 - ✓ Short acting (4 hrs) = ritaline
 - ✓ Extended release:
 - ❖ concerta (12 hrs)
 - ❖ metadateCD(8-10 hrs)
 - ❖ ritaline LA(8 hrs)
 - Side-effects: tics , sleep disorders , decreases appetite, headache, digestive problems.
 - amphetamines
 - ✓ Short acting (4 hrs)
 - ✓ Intermediate acting: Dexedrine (6 hrs)
 - non-stimulants →
 - atomoxetine HCL =strattera:
 - ✓ Selective norepinephrine reuptake inhibitor
 - ✓ S/E:dry mouth,nausea constipation ,sweating , dizziness, insomnia
 - catecholamine anti-depressants (2nd line) :
 - Imipramine and desipramine (tofranil and norpramin)
 - ✓ Duration of action → 24 hours
 - ✓ lower doses improve ADHD symptoms , higher doses improve depressive symptoms and mood swings
 - ✓ Side effects : nervousness , sleep problems ,fatigue , stomach upset , dizziness , dry mouth ,accelerate heart rate

Source: Dr. Amira's slides
Organized by: Raya Al-Majali

Headache

Sources: slides by Dr. Abdelkarim Al-Qudah and Nelson essentials

Epidemiology

- Headache is the most common reason that children are referred to child neurology practices.
- The prevalence of headache ranges from 37 to 51 percent in 7-year-olds, gradually rising to 57–82 percent by age 15
- The prevalence of migraine headache steadily increases through childhood and the male: female ratio shifts during adolescence.
- The prevalence of migraine rises from 3 percent at age 3–7 years to 4–11 percent by age 7–11, and up to 8–23 percent during adolescence.
- The mean age of onset of migraine is 7.2 years for boys and 10.9 years for girls

ICHD 3 (International Classification of Headache Disorders)

Part 1 (primary headaches)

1. Migraine

1.1 Migraine without aura

1.2 Migraine with aura

- ✓ Migraine with typical aura (visual, sensory, motor)
- ✓ Migraine with brainstem aura (vertigo, nausea, diplopia)
- ✓ Hemiplegic migraine
- ✓ Retinal migraine

1.3 Chronic migraine

- ✓ Headache occurring on 15 or more days per month for more than three months, which, on at least 8 days per month, has the features of migraine headache.

1.4 Complications of migraine

- ✓ Status migrainosus (> 72 HR)
- ✓ Persistent aura without infarction
- ✓ Migrainous infarction
- ✓ Migraine aura-triggered seizure

1.5 Probable migraine

1.6 Episodic syndromes that may be associated with migraine

2. Tension type headache

2.1 Infrequent episodic tension-type headache

- ✓ At least 10 episodes of headache occurring on <1 day per month

2.2 Frequent episodic tension-type headache

- ✓ At least 10 episodes of headache occurring on 1-14 days per month

2.3 Chronic tension-type headache

- ✓ ≥ 15 days per month

2.4 Probable tension-type headache

3. Trigeminal autonomic cephalalgias

3.1 Cluster headache

3.2 Paroxysmal hemicrania

3.3 Short-lasting unilateral neuralgiform headache attacks

3.4 Hemicrania continua

3.5 Probable trigeminal autonomic cephalgia

4. Other primary headache disorders

4.1 Primary cough headache

4.2 Primary exercise headache

4.3 Primary headache associated with sexual activity

4.4 Primary thunderclap headache

4.5 Cold-stimulus headache

4.6 External-pressure headache

4.7 Primary stabbing headache

4.8 Nummular headache

4.9 Hypnic headache

4.10 New daily persistent headache (NDPH)

Part 2 (secondary headaches)

1. Headache attributed to trauma or injury to the head and/or neck
2. Headache attributed to cranial or cervical vascular disorder
3. Headache attributed to non-vascular intracranial disorder
4. Headache attributed to a substance or its withdrawal
5. Headache attributed to infection
6. Headache attributed to disorder of homeostasis
7. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
8. Headache attributed to psychiatric disorder

Part 3 (painful cranial neuropathies, other facial pains and other headaches)

1. Painful cranial neuropathies and other facial pains
2. Other headache disorders

Diagnostic studies

- **Hx & PE.**
- **Imaging** – MRI +/- gadolinium contrast , CT
 - 1- when the neurologic examination is abnormal
 - 2- unusual neurologic features during the headache
 - 3- child has signs or symptoms of increased ICP
 - 4- Focal neurological deficits, alteration of consciousness
 - 5- chronic progressive headache.
- **lumbar puncture** - diagnostic and therapeutic of idiopathic intracranial hypertension

Migraine

- Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.
- In children and adolescents (aged under 18 years), attacks may last 2-72 hours.
- Associated symptoms include nausea, vomiting, pallor, photophobia, phonophobia, and desire to seek a quiet dark room for rest.
- Toddlers may exhibit irritability, sleepiness, pallor, and vomiting.
- Management:
 - ✓ Intermittent **symptomatic, or abortive**, analgesics (Acetaminophen or NSAIDs) are the mainstay for treatment. Symptomatic therapy requires early administration of an analgesic, rest, and sleep in a quiet, dark room.
 - ✓ If first-line medications are insufficient, triptan agents may be considered.
 - ✓ Triptans, (injectable, nasal spray, oral) are serotonin receptor agonists that may alleviate migraine symptoms.
 - ✓ Triptans are contraindicated for patients with focal neurological deficits associated with their migraines or signs consistent with basilar migraine (syncope) because of the risk of stroke.
 - ✓ Ergotamine drugs can be used as abortive treatment.
 - ✓ **Preventive therapy:**
 - TCA – tricyclic antidepressants (amitriptyline, nortriptyline)
 - AED – antiepileptic drugs (topiramate, valproic acid, Levetiracetam)
 - Antihypertensive agents (Propranolol, Clonidine)
 - CCB – calcium channel blockers (Nimodipine, flunarizine, verapamil)
 - Antihistamines (cyproheptadine)
 - ✓ Complementary and Alternative Treatments

Tension type headache

- Typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting minutes to days.
- The pain does not worsen with routine physical activity and is not associated with nausea, but photophobia or phonophobia may be present.
- Most common recurrent pattern of primary headaches in children and adolescents.
- Headaches can be related to environmental stresses or symptomatic of underlying psychiatric illnesses, such as anxiety or depression.
- Management:
 - ✓ The same general principles & medications used in migraine can be applied to children with TTHs
 - ✓ Simple analgesics (ibuprofen or acetaminophen) for acute treatment.
 - ✓ Flupirtine is a non-opioid analgesic that has been approved in Europe.
 - ✓ Amitriptyline has the most evidence of effective prevention of TTH.

Increased intracranial pressure (ICP) headache

- Increased ICP caused by a mass (tumor, vascular malformation) or intrinsic increase in pressure (pseudotumor cerebri).
- It is associated with vomiting, worse when lying down, on first awakening; awaken the child from sleep; remit on arising; exacerbated by coughing, Valsalva, or bending over.
- Examination may reveal– Papilledema, focal neurological deficits such as cranial nerve VI palsy.

Organized by: Asraa Alkubaisi & Rafeef Qawasmeh

Hematology & Oncology

Anemia

Anemia is not a final diagnosis; it is a diagnosis that leads to another diagnosis. So if you suspected anemia you should ask 4 questions:

1. Is the child anemic? If yes
2. What type of anemia?
3. What is the mechanism?
4. What is the underlying cause?

Anemia is defined as Hb or Hct > 2 standard deviations below the mean for age and gender.

Factors that determine hemoglobin levels:

1. Age: you should know the normal values for each age group.
2. Gender: males have higher values than females
3. Race. Blacks have higher ranges.
4. Degree of sexual maturation.
5. Altitude.

Rules to determine abnormalities of hemoglobin levels and MCV

- “The eleven plus point one rule”
 $11+1 \times (\text{age in years}) = \text{lower limit of normal for hemoglobin concentration.}$
- “The seventy plus one rule”
 $70+1 \times (\text{age in years}) = \text{lower limit of normal for MCV.}$

How is anemia diagnosed?

1. By routine screening.
2. Because of abnormal history, signs or symptoms (poor diet, pallor, jaundice etc).
3. Accidentally when performing a CBC for another reason.

How to approach anemia?

1. **History:** it is the most important part of diagnosis, you should ask about following:
 - Perinatal history: maternal diet.
 - Age of patient: the differential diagnosis is different according to age as following:
 - ✓ Neonatal age (DDx: blood loss, isoimmunization, congenital hemolysis or infection). They present with jaundice at birth and LBW.
 - ✓ 3-6 months (thalassemia syndromes).
 - ✓ 6-24 months (iron deficiency).
 - ✓ 3-15 years. (GIT blood loss, HS, G6PD).

- Duration: 2-3 days (think of hemolysis and blood loss)/ months (think of IDA).
- Nutrition and appetite.
- Prolonged exclusive breastfeeding (beyond 6 months). It is associated with increased risk of IDA.
- Jaundice? (Think of hemolytic anemia).
- Family history (thalassemia/ sickle-cell disease).
- Associated symptoms: SOB, dizziness
- Chronic illness, previous infection.
- Blood loss? (diarrhea, hematemesis, any bleeding)
- GERD? (GERD patients might come with anemia).
- Failure to thrive.
- Ask about puberty in females (menorrhagia might be the cause).
- Past medical history.

2. Physical examination:

- Vital signs, Height and weight.
- General appearance, Irritability.
- Signs of anemia (pallor, jaundice).
- Evidence of primary disease.
- Cardiovascular status.
- Hepatosplenomegaly, Lymphadenopathy, Bruising, café-au-lait spots.
- Signs of bone marrow failure syndrome (Fanconi anemia): skin pigmentation, deformities, short stature, abnormal faces.

3. Investigations:

- CBC including platelet count and differential WBC counts.
- Red blood cell indices: MCV, MCH and MCHC.
 - ✓ The most index is the MCV, it is important to measure what so called the Mentzer index.
 - ✓ Mentzer index = $MCV / RBC (\times 10^{12})$
 - ✓ This index differentiates the thalassaemia trait (Mentzer index < 12) from Iron deficiency anemia (Mentzer index > 13).
- Reticulocyte count:
 - ✓ If it is low then you should think of non-hemolytic causes (causes related to failure of production from the bone marrow) such as bone marrow suppression and aplastic anemia.
 - ✓ If it is high then you should think of hemolytic anemia, and the next step is to do Coombs test.

- Coombs test:
 - ✓ Positive test indicates autoimmune hemolytic anemia. In this case we give steroids. Avoid transfusion except in case of critical low hemoglobin (Hb <5).
 - ✓ Negative test indicates non-autoimmune hemolytic anemia. The next step is to order blood film.

- Blood film.
 - ✓ Heinz bodies: G6PD deficiency.
 - ✓ Spherocytes: spherocytosis (Do osmotic fragile test before transfusion).
 - ✓ Target cells: thalassemia or hemoglobinopathies. We do electrophoresis for diagnosis of hemoglobinopathies.

Physiologic anemia of infancy

- Fetal hemoglobin has high affinity to oxygen → release of O₂ to tissues is low → intrauterine hypoxia → compensation by high concentration of hemoglobin, [Hb] at birth = 18-19 g/dl.
- High FiO₂ at birth downregulates erythropoietin which results in progressive drop in Hb over first 2 – 3 months until tissue oxygen needs are greater than delivery.
- In term infants it has no associated problems and thus no treatment is needed. Typically nadir at 8 – 12 weeks to Hb of 9 – 11 g/dl.
- In preterm infants it is exaggerated and earlier; nadir at 3 – 6 weeks to Hb of 7 – 9 g/dl. They usually need transfusions depending on degree of illness and gestational age.

Other examples of physiologic anemia

1. Normal Hb level but the patient has cyanotic heart disease so the demands are not met.
2. Low hemoglobin in child with hypothyroidism. The demands are met so this is not a true anemia.

Iron deficiency anemia IDA

- Infants with decreased dietary iron typically are anemic at 9 – 24 months of age. This is caused by consumption of large amounts of cow milk and foods not enriched with iron. Therefore introducing iron rich foods is effective in prevention.
- Clinical appearances: pallor most common; also irritability, lethargy, pagophagia, tachycardia, systolic murmurs; long-term with neurodevelopmental effects.

- Laboratory findings:
 - ✓ First decrease in bone marrow hemosiderin (iron tissue stores), then decrease in serum ferritin → increased RDW → decreased serum iron → increased total iron binding capacity → decreased MCV → decreased MCH, low reticulocytes → anemia.
 - ✓ First hematological manifestation is increased RDW.
 - ✓ Microcytosis, hypochromia, poikilocytosis.
- Treatment:
 - ✓ Oral ferrous salts.
 - ✓ Limit milk, increase dietary iron.
 - ✓ Continue iron for 8 weeks after blood values normalize; repletion of iron in 1 – 3 months after start of treatment.

Acquired anemias:

1) Transient erythroblastopenia of childhood

- ✓ Transient hypoplastic anemia between 6 months – 3 years.
- ✓ Transient immune suppression of erythropoiesis.
- ✓ Often after nonspecific viral infection (not parvovirus B19).
- ✓ Normal MCV and HbF, decreased reticulocytes.
- ✓ Recovery within 1-2 months. Medication not helpful; may need one transfusion if symptomatic.

2) Anemia of chronic disease and renal disease

- ✓ Mild decrease in RBC lifespan and relative failure of bone marrow to respond adequately.
- ✓ Little or no increase in erythropoietin.
- ✓ Hb typically 6-9 g/dl, most normochromic and normocytic (but may be mildly microcytic and hypochromic).
- ✓ Treatment: control underlying problem, rarely need transfusions.

Hemolysis and hemolytic anemias

- Hemolysis is the premature destruction of erythrocytes. A hemolytic anemia will develop if bone marrow activity cannot compensate for the erythrocyte loss.
- Evidence of hemolysis: reticulocytosis/ increased LDH/ indirect hyperbilirubinemia/ hemoglobin concentration might be normal due to compensation by bone marrow/ low haptoglobin.
- Causes of hemolytic anemia:
 - ✓ Rh-incompatibility.
 - ✓ G6PD deficiency.
 - ✓ Hereditary spherocytosis.
 - ✓ Hemoglobin disorders (sickle cell anemia/ thalassemias).

1) Rh-incompatibility:

- ✓ The Rh factor (i.e. Rhesus factor) is a red blood cell surface antigen that was named after the monkeys in which it was first discovered. Rh incompatibility, also known as Rh disease, is a condition that occurs when a woman with Rh-negative blood type is exposed to Rh-positive blood cells, leading to the development of Rh antibodies.
- ✓ Once produced, maternal Rh immunoglobulin G (IgG) antibodies may cross freely from the placenta to the fetal circulation, where they form antigen-antibody complexes with Rh-positive fetal erythrocytes and eventually are destroyed, resulting in a fetal alloimmune-induced hemolytic anemia (not in the 1st baby).

2) Thalassemia

- Inherited microcytic hemolytic anemia due to abnormal Hgb synthesis.
- Normal predominant HbA is tetramer made up of 2 alpha globin chains and 2 beta globin chains. Human genome has 4 alpha globin genes and 2 beta globin genes.
- Thalassemia syndromes result when 1 or more of globin genes mutates; clinical phenotype determined by which and how many genes are mutated.
- Mutations are protective against malaria.
- Decreased production of either beta or alpha globin chains leads to relative excess of corresponding chains needed to form tetramer.
- **Beta thalassemia:**
 - ✓ Patients with beta thalassemia minor (1 beta gene mutated) are generally asymptomatic.
 - ✓ Patients with beta thalassemia major (mutations in both beta globin genes) will have typical dysmorphic facies due to extramedullary hematopoiesis and bone marrow expansion. They present in 2nd month of life with progressive anemia, hypersplenism, and cardiac decompensation. There are excess alpha globin chains which form alpha tetramers. Also, there is an increase in fetal Hb.
 - ✓ Treatment: chronic transfusions/ deferoxime/ may need splenectomy/ bone marrow transplant is curative.
- **Alpha thalassemia:**
 - ✓ It is due to impaired production of alpha chains from 1, 2, 3, or all 4 of the alpha globin genes, leading to a relative excess of beta globin chains.
 - ✓ 1 alpha gene mutation = silent carriers of alpha globin mutations.

- ✓ Hgb H disease: Two unstable hemoglobins are present in the blood: Hgb Barts (tetrameric γ chains) and Hgb H (tetrameric β chains). Both of them have a higher affinity for oxygen than normal Hb.

Alpha thalassemia		
Alpha thalassemia trait (minor)	Hgb H disease	Alpha thalassemia major
Deletion of 2 genes	Deletion of 3 genes	Deletion of 4 genes
Mild hypochromic, microcytic anemia (normal RDW) without clinical problems. Often diagnosed as IDA; need molecular analysis for diagnosis.	Easily diagnosed with electrophoresis. Microcytosis and hypochromia with mild to moderate anemia. Target cell & Heinz bodies present. Mild splenomegaly, jaundice & cholelithiasis. Neither transfusion nor splenectomy is required.	Severe fetal anemia resulting in hydrops fetalis. Newborn has predominantly Hgb Barts. Immediate exchange transfusions are required.

3) Sickle cell anemia

- Homozygous sickle cell or S-beta thalassemia.
- Autosomal recessive disorder of hemoglobin caused by point mutation of codon 6 of beta globin gene on chromosome 11, which results in substitution of 1 amino acid (valine instead of glutamic acid) resulting in production of sickle hemoglobin (HbS).
- HbS is less soluble than the normal adult hemoglobin (HbA) and, when deoxygenated, causes distortion in RBCs, which appear as sickle shapes. Sickle-shaped RBCs are prematurely destroyed, resulting in hemolytic anemia.
- Occurs in endemic malarial areas; carrier state is protective against malaria.
- No symptoms in newborn; development of hemolytic anemia over first 2-4 months (replacement of HbF); at 6 months some children have functional asplenia; by age of 5, all have functional asplenia.
- First presentation usually is hand foot syndrome (acute distal dactylitis); symmetric painful swelling of hands and feet.

Acute painful crisis	Vaso-occlusive crisis	Acute splenic sequestration	others
<p>Mostly extremities in younger ages.</p> <p>With ↑ age: head, chest, back and abdomen.</p> <p>Precipitated by illness, fever, hypoxia, acidosis, or without any factors (older).</p>	<p>Ischemic damage.</p> <p>Skin ulcers, retinopathy, avascular necrosis of hip & shoulder, infection of bone marrow, splenic autoinfarction.</p> <p>Acute chest syndrome, stroke, priapism.</p>	<p>Peak age 6 months to 3 years.</p> <p>Can lead to rapid death.</p> <p>Altered splenic function: increased susceptibility to infection (encapsulated bacteria)</p>	<p>Aplastic crisis – after parvovirus B19 infection; absence of reticulocytes.</p> <p>Cholelithiasis.</p> <p>Decreased renal function; UTIs; papillary necrosis.</p>

- Labs: ↑reticulocytes/ normal MCV/ blood smear in severe anemia: target cells, Howell-Jolly bodies, sickle RBC, markedly hyperplastic bone marrow.
- The best test to confirm diagnosis is Hb electrophoresis. Prenatal diagnosis for parents with trait.
- Treatment: prevent complications (pneumococcal and meningococcal vaccines, penicillin prophylaxis, folate supplementation, transfusions as needed, pain control, hydroxyurea, transcranial Doppler to monitor for risk of stroke, bone marrow transplant in selected patients age <16 years.

4) Glucose-6-phosphate dehydrogenase (G6PD) deficiency

- Two syndromes: episodic hemolytic anemia (most common) and chronic non-spherocytic hemolytic anemia.
- Caused by mutation in Gd gene on long arm of X chromosome and is inherited in X-linked pattern.
- Stresses associated with hemolytic crisis include:
 - ✓ Infection.
 - ✓ Ingestion of fava beans (favism).
 - ✓ Exposure to certain oxidative agents including many medications (acetylsalicylic acid, sulfa-containing drugs, antimalarials, and others).
- Acute hemolytic crisis can present with irritability progressing to fatigue and lethargy, fever, nausea, abdominal pain, or diarrhea and tea or cola-colored urine.
- Physical exam findings: signs of anemia/ signs of hemolysis: jaundice, tender splenomegaly, hepatomegaly/ in severe cases, signs of hypovolemic shock may be present/ Prolonged neonatal jaundice.
- Hemoglobinuria, Heinz bodies, increased reticulocytes, saturated haptoglobin. Diagnosis by direct measurement of G6PD activity.

- Treatment: prevention (avoid oxidants); supportive for anemia.

5) Hereditary spherocytosis

- Abnormal shape of RBC due to spectrin deficiency → decreased deformability → early removal of cells by spleen.
- Clinical presentation: anemia and hyperbilirubinemia in newborn/ hypersplenism/ biliary gallstones/ susceptible to aplastic crisis.
- Normal MCV, increased MCHC, increased reticulocytes, spherocytes or elliptocytes on smear (diagnostic).
- Osmotic fragility test for confirmation of diagnosis.
- Treatment: transfusions, splenectomy (after 5-6 years), folate.

Megaloblastic anemias

- Associated with macrocytosis; nucleated RBCs; large, hypersegmented neutrophils; hypercellular bone marrow with megaloblastic changes.
- Folate and vitamin B₁₂ are essential cofactors for erythropoiesis.

1. Folic acid deficiency:

- ✓ Sources of folic acid: green vegetables, fruits and animal organs.
- ✓ Peaks at 4 – 7 months of age.
- ✓ Causes: inadequate intake (pregnancy, goat milk feeding, chronic hemolysis)/ decreased absorption/ congenital defects of folate metabolism.
- ✓ Irritability, FTT and chronic diarrhea.
- ✓ Low serum folate.
- ✓ Treatment: daily folate; transfuse only if severe and symptomatic.

2. Vitamin B₁₂ (Cobalamine) deficiency:

- ✓ Only animal sources; produced by microorganisms. Not synthesized by humans.
- ✓ In infants born to mothers with deficiency, signs present in first 4-5 months.
- ✓ It is more commonly related to malabsorption than it is to nutritional deficiency (e.g. may be seen in Crohn's disease). Other causes are congenital pernicious anemia (AR, rare), juvenile pernicious anemia (rare) and gastric surgery; all these three are associated with lack of intrinsic factor which is necessary for the absorption of vitamin B₁₂.
- ✓ Normal serum folate and decreased vitamin B₁₂.
- ✓ Weakness, fatigue, irritability, glossitis, diarrhea, jaundice, many neurological symptoms.
- ✓ Treatment: parenteral B₁₂.

Bone marrow failure

The bone marrow failure syndromes include a group of disorders that can be either inherited or acquired. These diseases are disorders of the hematopoietic stem cell that can involve either 1 cell line or all of the cell lines (erythroid for red cells, myeloid for white blood cells, megakaryocytic for platelets). The lymphocytes, which are involved in lymphoproliferative disorders, are usually spared.

- Inherited disorders: Fanconi anemia/ Diamond-Blackfan anemia.
- Acquired disorders: the most common cause of acquired bone marrow failure is aplastic anemia.

1) Fanconi anemia

- Not at birth; the most common age of presentation is 5 – 6 years.
- Physical abnormalities: hyperpigmentation and café-au-lait spots/ short stature/ petite/ cardiac and renal anomalies/ absent or hypoplastic thumbs/ squint/ ear abnormalities/ abnormal faces.
- Congenital pancytopenia.
- Treatment: corticosteroids and androgens/ bone marrow transplant is definitive.

2) Diamond-Blackfan anemia (congenital pure red cell anemia)

- Increased RBC programmed cell death that leads to profound anemia by 2-6 months.
- Short stature/ craniofacial deformities/ triphalangeal thumbs.
- Macrocytosis/ very low reticulocyte count/ increased serum iron.
- Treatment: corticosteroids/ transfusions and deferoxamine/ splenectomy; mean survival 40 years without stem cell transplant/ stem cell transplant (definitive).

Pancytopenia

It is a medical condition in which there is a reduction in the number of red and white blood cells, as well as platelets. (According to Dr. Issam Haddad it is the reduction of more than one element, not necessarily all of them).

Causes of pancytopenia:

- CMV, parvovirus: (most common cause/ suppression of bone marrow/ atypical lymphocytosis in blood film/ supportive treatment).
- Leukemia/ lymphoma/ Neuroblastoma: bone marrow infiltration.
- Myelodysplastic syndrome (myeloproliferative disorders).
- Vit-B12 deficiency/ Folate deficiency: if 1-month infant has B12 deficiency, then mother has B12 deficiency.

- Aplastic anemia (causes bone marrow failure).
- Drugs: chemotherapy/ anticonvulsants/ chloramphenicol: an antibiotic for meningitis can cause aplastic anemia, not used anymore.

Microcytic anemias	Normocytic anemias	Macrocytosis
<p>Most common: Iron deficiency/ Thalassemia</p> <p>Less common: Anemia of inflammation/ Hemoglobin C disease/ Hemoglobin E disease/ Hereditary pyropoikilocytosis/ (Lead poisoning)</p> <p>Rare: Sideroblastic anemia/ Copper deficiency/ Congenital atransferrinemia</p>	<p>Problems in production: - Anemia of chronic disease. - Bone marrow failure. - Transient erythroblastopenia of childhood.</p> <p>Problems in destruction: -Hemorrhage. - Consumption (hypersplenism, hemangioma). - Hemolysis (congenital and acquired).</p>	<p>- Normal newborn infant. - Reticulocytosis. - Marrow failure. - Drugs. - Cyanotic congenital heart disease. - Down syndrome. - Hypothyroidism. - Liver disease. - Megaloblastic anemia (B₁₂, folate deficiency).</p>

RDW	MCV		
	Low	normal	high
Normal	Heterozygous alpha and beta thalassemia / chronic disease	Chronic disease	Aplastic anemia
High	Iron deficiency/ hemoglobin H disease/ S beta thalassemia	Liver disease	Folate/ B12 deficiency

Done by: Rafeef Qawasmeh

Special thanks to Anwar Jaber for some notes

This sheet includes notes from Dr. Issam Haddadin and some topics from Kaplan, in addition to some notes from the old slides.

Bleeding disorders

First part of sheet is considering approach to bleeding disorders through a case. This part is totally dependent on notes from Dr. Issam Haddadin.

5 year old child presented with epistaxis and purpuric rash. How to approach this patient?

- Purpuric rash: usually after trauma/ doesn't disappear on pressure unlike urticarial which disappears.
- In history you have to ask about following :
 - ✓ Bone ache and joint pain: to rule out leukemia.
 - ✓ Liver disease/ renal disease: may cause bleeding.
- You have to examine lymph nodes, spleen and liver to rule out malignancy.

Investigations:

1. CBC: results showed thrombocytopenia (low platelet count)

DDx of thrombocytopenia:

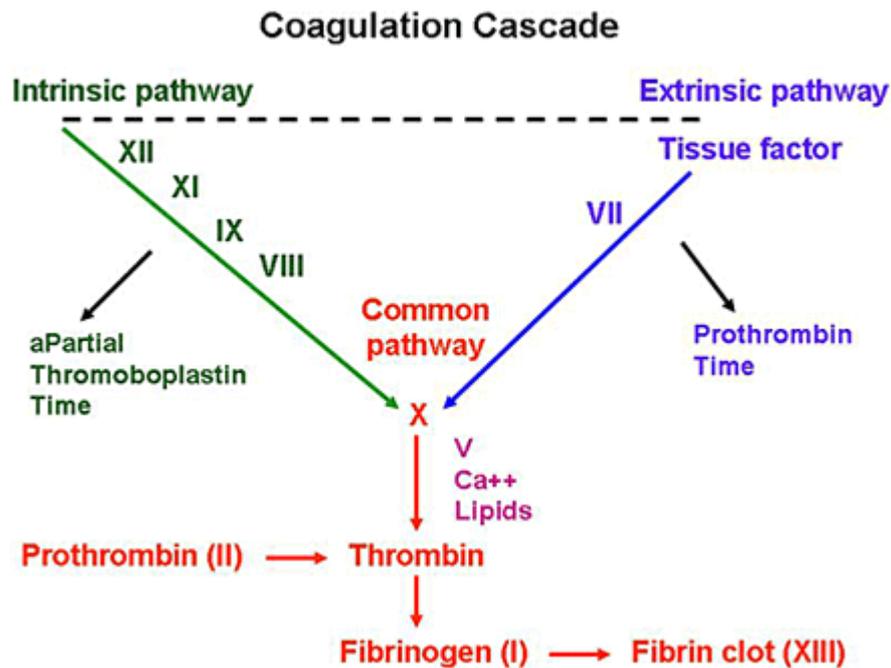
- Bone marrow failure (platelets are 1st to decrease).
- Immune thrombocytopenic purpura.

2. Blood film:

- Presence of Giant platelets on blood film means that bone marrow is functioning (no bone marrow failure).

3. If CBC was normal, do PT and PTT

- Prothrombin time PT: normal range 11-14 seconds/ for extrinsic pathway of blood coagulation.
- Partial thromboplastin time PTT: normal range 25-35 seconds/ for intrinsic pathway.
- INR: International normalized ratio = $\frac{PT\ patient}{PT\ control} \times 12\ seconds$.
- If PTT is high → do factor assay starting with factor VIII
 - ✓ Factor VIII deficiency: hemophilia A (most common).
 - ✓ Factor IX deficiency: hemophilia B
 - ✓ Factor XI deficiency: hemophilia C



- Factor XIII: fibrin stabilizing factor.
- We do clot solubility test for factor 13: clot in solution must be 75% stable >> if factor 13 is deficient >> lysis of the clot.
- Factor XIII deficiency noticed in newborn as delayed separation of umbilical cord.
- Factor VII has the shortest half-life (2 hours).

4. If CBC, PT, PTT, INR are normal, what is next step?

Do **bleeding time** for platelet dysfunction.

- Normal bleeding time 3-8 minutes.
- Causes of prolonged bleeding time (platelet dysfunction): vasculitis/ Von Willebrand disease/ thrombocytopenia/ Glanzmann's thrombasthenia/ Bernard-Soulier syndrome.
- Platelet dysfunction: defect in the cell wall or granules/ (problem in platelet aggregation or adhesion).
- Life span of platelet is 7 days.
- Platelets normally have no nuclei.
- Treatment: give platelet for lifelong in severe bleeding (GI or CNS bleeding).

Now, let's start with the second part of sheet which discusses some specific topics in bleeding disorders. This part includes notes from the doctor and summary of Kaplan.

Immune thrombocytopenic purpura (ITP)

- Platelet disorder; antibodies against platelet surface → destruction of platelets in spleen → thrombocytopenia.
- Antibodies production typically 1-4 weeks after a non-specific viral infection.
- Clinical presentation: sudden onset of petechiae and purpura with or without mucous membrane bleeding. Normal examination.
- Labs: platelets $< 20,000/\text{mm}^3$, platelet size normal to increased, other cell lines normal, bone marrow-normal to increased megakaryocytes.
- Management: admission/ IV lines/ cross match/ steroids to suppress antibody production/ IVIG block the receptor sites on spleen to prevent destruction of platelets.
- Prognosis: 75% success rate/ 25% resistant.
- Chronic ITP: thrombocytopenia persisting >6 months following initial diagnosis.
- No need for bone marrow biopsy in acute ITP.
- In chronic ITP we do bone marrow examination and look for systemic diseases (e.g. SLE could present initially with ITP).

Hemophilia

- Defect in intrinsic factors: VIII (hemophilia A), IX (hemophilia B), XI (hemophilia C).
- Very common in Jordan.
- X-linked.
- Slowing of rate of clot formation; easy bruising with crawling and walking/ bleeding into joints (hemarthroses) is the hallmark. It can cause joint damage.
- Labs: increase in PTT (all others normal)
- Treatment: give prophylaxis (synthetic factors/ plasma-derived factors): 2 times/ week. Avoid antiplatelet and aspirin medications. DDAVP (desmopressin) increases factor VIII levels in mild disease.

Von Willebrand disease (vWD)

- It is the most common hereditary bleeding disorder; AD; more in females.
- Von Willebrand factor (vWF) in normal situation adheres to subendothelial matrix, and platelets then adhere to this and become activated; also serves as carrier protein for factor VIII. This factor is defective in this disease.
- Mucocutaneous bleeding (excessive bruising, epistaxis, menorrhagia, postoperative bleeding).

- Increased bleeding time and PTT.
- Treatment: increase the level of vWF and factor VIII

Vitamin K deficiency

- Newborn needs intramuscular administration of vitamin K or develops bleeding diathesis.
- Vitamin K is fat soluble so deficiency associated with a decrease in factors II, VII, IX, and X, and proteins C and S.
- Increased PT and PTT with normal platelet count and bleeding time.

Liver disease

- Decrease in clotting factors production proportional to extent of hepatocellular damage.
- All clotting factors are produced exclusively in the liver, except for factor VIII.
- Treatment: fresh frozen plasma (supplies all clotting factors) and/or cryoprecipitate (supplies fibrinogen).

Oncology part

Leukemia

- It is the most common tumor in children.
- Clonal expansion and arrest at a specific stage of normal myeloid or lymphoid hematopoiesis.
- Peak age at 3 – 5 years (same as peak age of viral infection).

Types of leukemia:

- 1- Acute lymphoblastic leukemia (ALL); the most common type in children.
- 2- Chronic lymphoblastic leukemia (CLL).
- 3- Acute myelogenous leukemia (AML).
- 4- Chronic myelogenous leukemia (CML).

Acute lymphoblastic leukemia (ALL)

Presentation:

- Systemic effects: fever, pallor and weakness.
- Bone ache: backache, joint pain especially lower extremities.
- Signs and symptoms of bone marrow failure: bleeding (bruising, epistaxis, petechial, purpura, mucous membrane bleeding), lymphadenopathy, hepatosplenomegaly, and joint swelling.
- Painless testicular enlargement.
- CNS involvement.
- Chloroma: it is a solid collection of leukemic cells occurring outside of the bone marrow.
- Wide mediastinum (due to infiltration to thymus).
- Lung infiltrate.

Diagnosis:

- CBC and blood film:
 - ✓ WBC could be high, normal or low.
 - ✓ Blast cells on blood film (the most important).
- LFT & KFT (mainly LDH).
- CXR / abdominal ultrasound.
- Bone marrow biopsy: from back (not sternum) / for morphology, cytochemistry, cytogenetic and flow cytometry.
- CSF examination.

Immunophenotypes of ALL:

- Precursor-B cell ALL (the most common).
- T-cell ALL.
- Mature B cell ALL.
- Chromosomal translocation t (9; 22).

Prognostic factors in ALL	High risk	Low risk
Age	> 10 years, <1 year	1 – 10 years
WBC count	>50,000	<50,000
Cytogenetic	T-cell ALL , t(4: 1), t(9:22)	t(12:21)
DNA index	< = 1.16	>1.16
CNS involvement	Present	Absent
Response to chemotherapy	Slow and late response	Rapid and early response

Treatment of ALL:

- Prepare patient: blood culture/ antibiotics/ hydration.
- Induction chemotherapy: VCR/ steroids/ Adriamycin.
- Consolidation chemotherapy.
- Maintenance chemotherapy.
- Intrathecal methotrexate (duration: 2.5-3 yrs) / prophylaxis.

Complications:

- Majority is relapse:
 - ✓ Bone marrow is the most common site of relapse.
 - ✓ CNS (the 2nd): increased ICP or isolated nerve palsies.
 - ✓ Testicular relapse.
- Pneumocystis pneumonia.
- Other infections because of immunosuppression.
- **Tumor lysis syndrome** – features: hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcaemia.

Acute myeloid leukemia (AML)

- Presentation: same as ALL but less likely to have hepatosplenomegaly and lymph node enlargement.
- Diagnosis: bone marrow examination.
- Treatment: very intensive chemotherapy of 6 months duration/ bone marrow transplantation.
- FAB classification:
 - ✓ You have to know about M3 subtype (Acute promyelocytic leukemia (APL)). It has a good prognosis.
 - ✓ Beyond M3: bad, bone marrow transplantation is needed.

M0	Undifferentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia with minimal maturation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M4eos	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryocytic leukemia

Chronic myeloid leukemia (CML)

- Age (10-12 yrs).
- Transformation to acute: big threat.
- Splenomegaly.
- Positive Philadelphia chromosome.
- ↑ differentiating myeloid.
- Treatment:
 - ✓ Imatinib (Glivec): excellent but expensive/ tyrosine kinase inhibitor.
 - ✓ Hydroxyurea.
 - ✓ Busulfan.
 - ✓ Bone marrow transplant: definite treatment/ before transformation.

Lymphoma

Lymphoma is a group of blood cell tumors that develop from lymphatic cells.

Differential diagnosis:

- Inflammatory: bacterial lymphadenitis/ viral lymphadenitis.
- Granulomatous diseases: cat scratch disease/ atypical mycobacterium.
- Reactive hyperplasia: Kawasaki disease/ mononucleosis.
- Neoplastic: Hodgkin/ non-Hodgkin/ neuroblastoma.

General notes:

- Any intussusception above age of 2 years: think of lymphoma (abdominal lymphoma).
- Brain lymphoma: rule out HIV.
- Renal lymphoma: renal failure presentation.
- Differential diagnosis of any lytic bone lesion: lymphoma/ neuroblastoma/ metastases.
- Chemotherapy is the mainstay of treatment.
- Surgery is not for treatment, but for diagnosis (to remove a lymph node for testing (biopsy)).

Stages of lymphoma:

- Stage I: 1 group of lymph nodes.
- Stage II: 2 or more groups of lymph nodes on the same side of (above or below) the diaphragm
- Stage III: The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
- Stage IV: bone marrow or CNS involvement.

Sub-stages of lymphoma:

- Stage A: no B symptoms.
- Stage B: presence of B symptoms.
- B symptoms: systemic symptoms of fever, night sweats, and weight loss.

Emergencies associated with lymphoma:

- Spinal cord compression: must be diagnosed and treated ASAP.
- Respiratory distress.
- **Tumor lysis syndrome:** rapid development of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute renal failure/ oliguria/ fluid retention.

- ✓ Management of tumor lysis syndrome: hydration/ alkalinization with NaHCO₃/ allopurinol.

Hodgkin lymphoma

- Most in 15- to 19- year old.
- Diagnostic hallmark: Reed-Sternberg cell (large cell with multiple or multilobulated nuclei).
- Histologic types:
 - ✓ Lymphocytic predominant.
 - ✓ Nodular sclerosing.
 - ✓ Mixed cellularity.
 - ✓ Lymphocyte depleted; now considered to be a high-grade non-Hodgkin lymphoma.
- Clinical presentation:
 - ✓ Painless, firm cervical or supracervical nodes (most common presenting sign).
 - ✓ Anterior mediastinal mass.
- Diagnosis: excisional biopsy of node.

Non-Hodgkin lymphoma

- Malignant proliferation of lymphocytes of T-cell, B-cell, or intermediate-cell origin.
- Predisposition with congenital or acquired immunodeficiencies.
- It is the most common type of lymphoma in children/ very aggressive unlike in adults.
- Subtypes:
 - ✓ Burkitt lymphoma: B-cell lymphoma/ EBV plays a major role/ starry sky appearance.
 - ✓ Lymphoblastic lymphoma: usually T-cell, mostly mediastinal masses.
 - ✓ Large B-cell lymphoma.
 - ✓ Large T-cell lymphoma.
 - ✓ Anaplastic large cell lymphoma.
- Presentation: anterior mediastinal mass (respiratory symptoms), abdominal mass and pain.
- Diagnosis: biopsy.

Brain tumors

- Brain tumor is the 2nd most frequent malignancy in children.
- Most common < 7 years of age.
- Symptoms depend on location.
- Head CT scan is the best initial test.
- Subtypes:
 - 1- Infratentorial:
 - ✓ Most common.
 - ✓ Low grade; rarely invasive.
 - ✓ Types: juvenile pilocytic astrocytoma (m.c, classic site is cerebellum), medulloblastoma, ependymoma, brain stem tumors, malignant astrocytoma.
 - 2- Supratentorial:
 - ✓ Craniopharyngioma (m.c).
 - ✓ Optic nerve glioma.

Other malignancies

Wilms tumor

- **Nephroblastoma**; it is the 2nd most common malignant abdominal tumor.
- Usual age 2 – 5 years.
- One or both kidneys (bilateral in 7%).
- Associations: hemihypertrophy/ aniridia/ genitourinary anomalies.
- May be a part of WAGR syndrome (wilms/ aniridia/ genitourinary malformations/ mental retardation).
- Presentation:
 - ✓ Asymptomatic abdominal mass (in 80% of children at presentation).
 - ✓ Abdominal pain or hematuria (25%).
 - ✓ Urinary tract infection and varicocele (less common).
 - ✓ Hypertension, gross hematuria, and fever (5-30%).
 - ✓ Hypotension, anemia, and fever (from hemorrhage into the tumor; uncommon).
 - ✓ Respiratory symptoms related to lung metastases (in patients with advanced disease; rare).
- Diagnosis: ultrasound is the best initial test. Abdominal CT for confirmation.
- Treatment: surgery, then chemotherapy and radiation.

Neuroblastoma

- From neural crest cells, due to N- myoncogene; can occur at any site.
- Firm, palpable mass in flank or midline; painful; with calcification and hemorrhage.
- Initial presentation often as metastases – long bones and skull, orbital bone, bone marrow, lymph nodes, liver, skin.
- They can present with ataxia or opsomyoclonus (dancing eyes and dancing feet). These patients may also have Horner syndrome.
- Diagnosis:
 - ✓ Plain X-ray, CT scan, MRI.
 - ✓ Elevated urine homovanillic acid (HVA) and vanillylmandelic acid (VMA) in 95% of cases.
- Treatment: surgery/ chemotherapy and radiation/ stem cell transplant (definitive).
- It usually crosses the midline; while Wilm's tumor doesn't.

Pheochromocytoma

- Catecholamine secreting tumor from chromaffin cells.
- Most common site is adrenal medulla, but can occur anywhere along abdominal sympathetic chain.
- AD; associated with neurofibromatosis, MEN-2A and MEN-2B, tuberous sclerosis, Sturge-Weber syndrome, and ataxia telangiectasia.
- Clinical presentation: episodic severe hypertension, palpitations and diaphoresis, headache, abdominal pain, pallor, vomiting, sweating, encephalopathy.
- Retinal examination: papilledema, hemorrhage, exudate.
- Diagnosis:
 - ✓ CT scan is the best initial test.
 - ✓ MBIG scan.
 - ✓ Labs: increase in blood or urinary levels of catecholamines and metabolites.
- Treatment: removal of the tumor (high risk)/ preoperative alpha and beta blockade and fluid administration/ prolonged follow up.

Rhabdomyosarcoma

- The name is derived from the Greek words rhabdo, which means rod shape, and myo, which means muscle. As the name suggests, the tumor is believed to arise from a primitive muscle cell.
- Almost any site; which determines presentation.
- Increased frequency in neurofibromatosis.
- Types:
 - ✓ Embryonal (60%) – intermediate prognosis.
 - ✓ Botryoid – vagina, uterus, bladder, nasopharynx, middle ear.
 - ✓ Alveolar – very poor prognosis/ trunk and extremities.
- Presentation: mass that may or may not be painful/ displacement or destruction of normal tissue/ easily disseminates to lung and bone.
- Diagnosis: biopsy, CT, MRI, bone scan.
- Treatment: best prognosis with completely resected tumors (but most are not completely resected)/ chemotherapy pre- and postoperatively/ radiation.

Done by: Rafeef Al-Qawasmeh

Oncology sheet included notes from Dr. Issam Haddadin and some topics from Kaplan.

Tumor lysis syndrome

Tumor lysis syndrome may occur secondary to release of intracellular components into the bloodstream as a result of tumor cell death after chemotherapy. It occurs mainly in acute leukemias and non-Hodgkin lymphomas (especially Burkitt's lymphoma) but can also occur in other hematologic cancers and after steroid therapy and, uncommonly, after treatment of solid tumors. It should be suspected in patients with a large tumor burden who develop acute kidney injury after initial treatment.

The diagnosis is confirmed by some combination of the following findings:

- Renal failure
- Hypocalcemia (< 8 mg/dL)
- Hyperuricemia (> 15 mg/dL)
- Hyperphosphatemia (> 8 mg/dL)
- Hyperkalemia (>5.2 mg/dL)

Treatment:

Hyperuricemia:

- rasburicase(an enzyme that oxidizes uric acid to allantoin (a more soluble molecule)), may be used also to prevent tumor lysis, also we use Vigorous IV hydration.
- Allopurinol (It is a xanthine oxidase inhibitor ,It prevents the production of new uric acid molecules, so It **does not** decrease the uric acid concentration that is already have been in the blood stream) can be used to prevent the progression of hyperurecemia.
- Patients who have a cancer with rapid cell turnover should receive allopurinol for at least 2 days before and during chemotherapy; for patients with high cell burden, this regimen can be continued for 10 to 14 days after therapy. All such patients should receive vigorous IV hydration to establish a diuresis of at least 100 mL/h before treatment.
- Although some physicians advocate NaHCO₃ IV to alkalinize the urine and increase solubilization of uric acid, alkalinization may promote Ca phosphate deposition in patients with hyperphosphatemia, and a pH of about 7 should be avoided.

*Think of electrolyte disturbances in this way:
intracellular Potassium phosphate and uric acid increases in the blood stream after the cell lysis then Phosphate binds (Ionic bonding) to free serum calcium*

Rasburicase is contraindicated in patients with Asthma, G6PD and in methemoglobinemia

Hyperkalemia:

- >5.3: give K xylate.
- >6: check ECG and give calcium gluconate and insulin with glucose.

Hyperphosphatemia:

- Treat with calcium gluconate.

Hypocalcemia:

- Do not treat unless there are symptoms of hypocalcemia.

Done by: Mohannad Abohamad

Cardiology

Cardiac examination

This sheet was written from Dr. Laila Totanji seminar notes.

General inspection:

- Level of consciousness (alert, oriented)
- **Signs of distress** (tachypnea/ use of accessory muscles/ dyspnea/ cyanosis/ nasal flares/ grunting).
 - ✓ Grunting: against partially closed glottis/ if completely closed: Valsalva.
 - ✓ Central cyanosis causes: respiratory problems/ cardiac problems/ CNS problems/ reflux/ methemoglobin.
 - ✓ Peripheral cyanosis: vasoconstriction.
 - ✓ Central cyanosis is always combined with peripheral cyanosis.
 - ✓ Clubbing combines central cyanosis only if the latter has been for at least 6 months.
- **Color:**
 - ✓ Pallor (look at conjunctiva).
 - ✓ Jaundice (sclera).
 - ✓ Malar rash.
 - ✓ Cyanosis.
- **Dysmorphic features:**
 - ✓ Cleft lip/ cleft palate.
 - ✓ Palpebral fissure/ epicanthal folds/ hypertelorism.
 - ✓ Abnormalities during lateral orientation in embryo (if found on face, look for abnormalities in internal organs).

Vital signs:

- **Temperature:** hypothermia may cause bradypnea and/or bradycardia. Sometimes when you correct the hypothermia, HR & RR will back to normal. So you have to rewarm patients before you can say they are dead!
- **Heart rate HR:** in newborn it is between 90 – 180 / the lower limit reaches its lowest number (60) at age of 18.
- **Respiratory rate (RR):**
 - ✓ Decreases with age (stroke volume and lung surface area increase with age).
 - ✓ Newborn (30 - 60)
 - ✓ 1 year of age (40)
 - ✓ 2 years (35)
 - ✓ Adults (20)

- **Blood pressure (BP):**
 - ✓ Systolic blood pressure in lower limb is higher than that of upper limb by 10 mmHg. This is due to peripheral amplification (increased elastic recoil in lower limbs).
 - ✓ Before the age of 4 years, there must be full screening for BP (upper and lower limbs).

Growth parameters:

- Crossing 2 major lines after age of 2 years is abnormal.
- Children with congenital heart disease (CHD) are at increased risk for poor growth.
- Congenital heart disorders in relation to growth parameters:
 - ✓ **Volume overload (normal height/ low weight):**
 - Opening in heart without obstruction.
 - Mainly on right side.
 - AV canal/ moderate to large VSD/ PDA.
 - ✓ **Cyanotic (↓ weight and height):**
 - Opening with obstruction or abnormal connection.
 - Tetralogy of fallot (most common).
 - Transposition of vessels.
 - Tricuspid atresia.
 - ✓ **Pressure overload (no change in weight or height):**
 - Silent killer/ asymptomatic.
 - Mild to moderate coarctation.
 - If severe >> leads to CHF >> symptomatic.

Exposure/ inspection:

- Stand at foot of patient.
- Inspect for subcostal retraction/ intercostal retraction/ suprasternal retraction/ symmetry.
- Deformities: pectus excavatum/ pectus carinatum.
- Surgical scars: midline sternotomy scar or lateral thoracotomy scar indicate heart surgery.
- GI surgical scars indicate GI abnormalities, which increase the chance of cardiac abnormalities.

Palpation:

- Stand at right side of patient.
- 4 cardiac areas (same as adults).

- Apex beat: at 4th intercostal space lateral to the midclavicular line (in infants)/ at age of 12: reaches adult's level.
- Thrill: big pressure difference + small hole >> turbulence >> indicates moderate to severe stenosis (pulmonary/ aortic).
- Tricuspid and mitral valves rarely stenosed in pediatrics.
- Thrill of VSD at tricuspid area is a good sign in VSD patient.
- Right/ left ventricular heave: pressure or volume overload.

Auscultation:

- At supine position: auscultate with the diaphragm then bell at the 4 areas.
- At left lateral decubitus position: 4 areas/ left axilla for mitral stenosis or regurgitation.
- At sitting position: 4 areas.
- While patient leaning forward and holding breath, auscultate under the pulmonary area for aortic regurgitation.
- Neck: site of radiation of anything in aortic valve.
- Interscapular area: site of radiation of anything from pulmonary valve.
- Mitral stenosis/ regurgitation: think of rheumatic heart disease.
- Auscultation of lung: anteriorly for abnormalities in middle lobes/ posteriorly (on back) for abnormalities in lung from apex to base.

Vascular examination:

- Pulses: radio-pedal or radio-femoral / significant delay indicates coarctation.
- Edema.
- Capillary refill (at toes/ <= 2 seconds)/ compromised in heart failure and post-operative cardioplegia.

Heart sounds:

- S1/S2
- S2 split: normally during inspiration.
- Abnormal splitting:
 - ✓ Paradoxical split: during expiration (severe aortic stenosis).
 - ✓ Fixed wide splitting (ASD).
 - ✓ Increased intensity of P2 (pulmonary HTN).
- S3 can be normal in children and pregnant.
- S4: always pathological sound (heard just before S1).
- Tachycardia + S3 or S4 = gallop.
- Tachycardia + S3 + S4 = summation gallop.
- Tachycardia + hepatomegaly = heart failure until proven otherwise.

- Tachycardia + hepatomegaly + gallop = decompensated heart failure.

Murmurs:

- Assess the grade, timing and character.
- Diastolic murmurs:
 - Early: after S2/ decrescendo murmur/ low pitched/ indicates aortic or pulmonary regurgitation.
 - Mid-to-late: before S1/ indicates mitral or tricuspid stenosis which are rare in pediatrics.
- Systolic murmurs:
 - Ejection systolic murmur: after S1/ crescendo-decrescendo murmur/diamond in shape/ indicates aortic or pulmonary stenosis.
 - Pansystolic murmur: masks the S1/ mitral regurgitation/ tricuspid regurgitation/ VSD at tricuspid area.
- Normal murmurs (innocent):
 - Also known as functional, insignificant, or flow murmurs.
 - Usually heard on routine physical examination; ↑ with fever, infection, anxiety and anemia.
 - Never with thrill; never greater than grade 2/6
 - Ejection systolic; never diastolic.
 - Vibratory, soft and musical.
 - Around tricuspid area.
 - Not crescendo-decrescendo murmur.

Cardiac evaluation

These are notes from Dr. Iyad Al-ammouri seminar

What are the parameters/tests/ findings that can be used to evaluate cardiac function?

1. Cardiac output (CO): it is a term used in cardiac physiology that describes the volume of blood being pumped by the heart per unit time. It can be referred to as pump function or perfusion.
 - $CO = HR \text{ (heart rate)} \times SV \text{ (stroke volume)}$
 - $CO = BP / R \text{ (resistance)}$
2. Pulse volume: it gives an impression about resistance, and thus the cardiac output.
3. Capillary refill: it gives an impression about resistance; prolonged capillary refill indicates high resistance.
4. Temperature: it gives an impression about resistance; decreased peripheral temperature (cold extremities) indicates high resistance.
5. Gallop rhythm: may indicate heart failure.
6. Pulse oximetry (oxygen saturation): it tells little about cardiac function. It rather gives an impression about pulmonary function.
7. Respiratory rate: tachypnea in cardiac patients is mostly due to pulmonary edema or metabolic acidosis and not cardiac problem itself, so it doesn't tell that much about cardiac function.
8. Murmurs: do not tell about cardiac function.
9. Ejection fraction:
 - Assessed by echocardiogram.
 - $Ejection\ fraction = (EDV - ESV) / EDV$
 - It should be more than 60% to be considered normal in children.
 - Limitations:
 - ✓ May be normal in presence of cardiac problems (when both EDV and ESV are normal).
 - ✓ HR is not taken into consideration.
 - ✓ It doesn't tell about systemic output (PDA, VSD).
10. ABGs/lactic acid: good for 1 hour - to - 1 hour management.
11. C.W.P / CVP: invasive monitors with many complications.
12. Brain natriuretic peptide or B-type natriuretic peptide (BNP): is a 32-amino acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells.

- For very fast rhythms: Rate = 1500 / number of small squares in between each consecutive R wave.
- For slow or irregular rhythms: Rate = number of complexes on the rhythm strip x 6 (this gives the average rate over a ten-second period).

Axis:

- The most efficient way to estimate axis is to look at leads I + aVF.
- Left axis deviation: tricuspid atresia/ endocardial cushion defect.

LEAD I	LEAD AVF	QUADRANT	AXIS
Positive	Positive	Left lower quadrant	Normal (0 to +90 degrees)
Positive	Negative	Left upper quadrant	Possible LAD (0 to -90 degrees)
Negative	Positive	Right lower quadrant	RAD (+90 to 180 degrees)
Negative	Negative	Right upper quadrant	Extreme Axis Deviation (-90 to 180 degrees)

QRS complex:

- 0.08 – 0.12 seconds.
- Prolonged terminal branch indicates bundle branch block.
 - V1, V2: to assess right ventricle.
 - V5, V6: to assess left ventricle.
 - Positive prolongation = prolonged upward deflection.
 - Negative prolongation = prolonged downward deflection.
 - Positive prolongation of terminal branch in V1, V2 = right bundle branch block.
 - Negative prolongation in V1, V2 = left bundle branch block.
 - Positive prolongation in V5, V6 = left bundle branch block.
 - Negative prolongation in V5, V6 = right bundle branch block.
- Prolonged 1st part of QRS = delta wave = Wolff-Parkinson-White syndrome = accessory AV pathway.
- Prolongation of all parts of QRS (diffuse prolongation) = anything affecting the whole ventricle (e.g. dilated cardiomyopathy).

✚ PR interval:

- 0.16 seconds.
- DDX of prolonged PR:
 - 1st degree heart block.
 - Myocarditis (rheumatic or viral).
 - Digitalis toxicity.
 - ASD, endocardial cushion defect, Ebstein's anomaly.
- ↓ PR: pre-excitation (the presence of an accessory pathway between the atria and ventricles, e.g. Wolff-Parkinson-White syndrome)/ glycogen storage disease.

✚ QT interval:

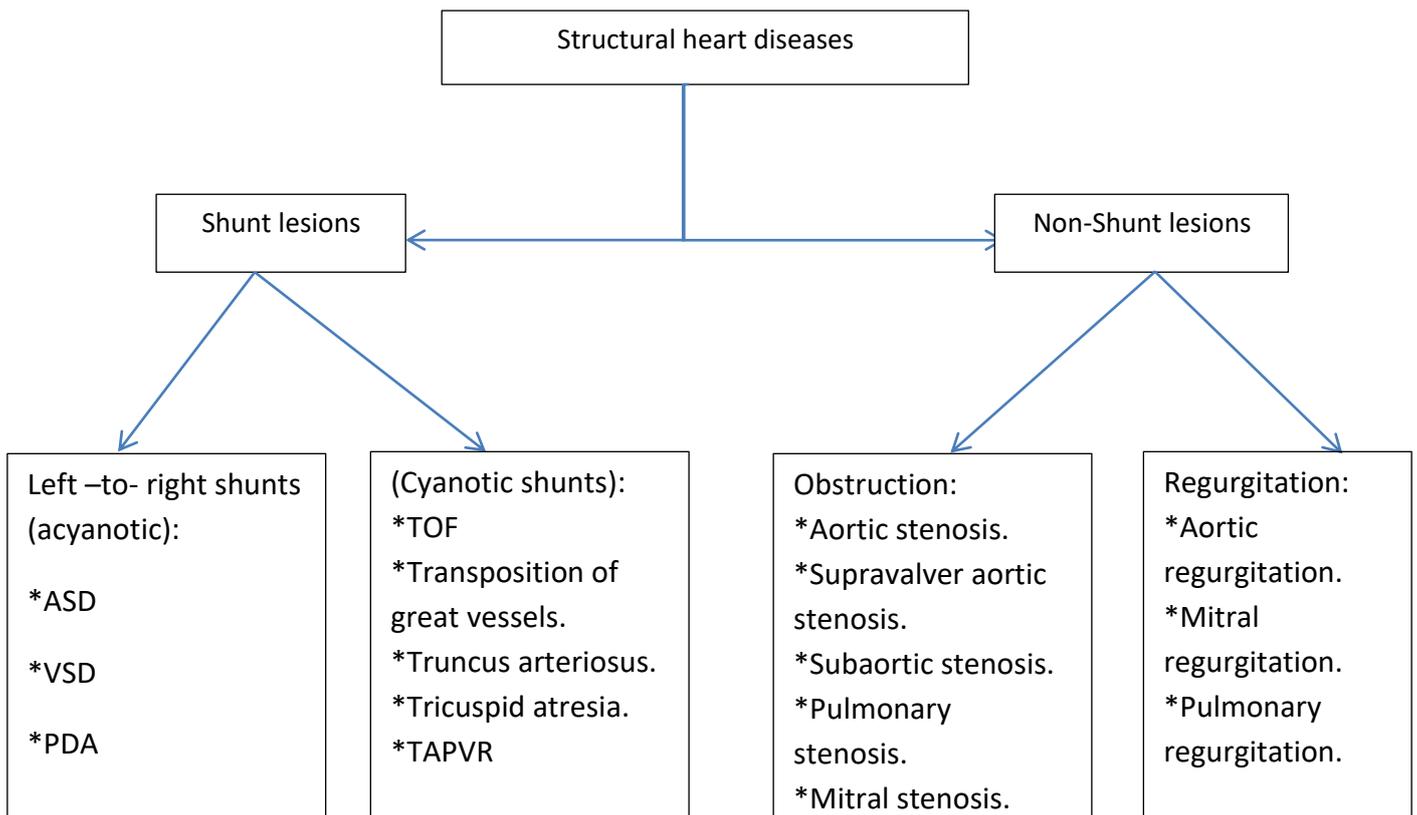
- QTc (corrected QT interval for heart rate) =
 $QT \text{ (measured)} / \sqrt{\text{preceded RR}}$
- RR is the interval from the onset of one QRS complex to the onset of the next QRS complex. (RR interval = 60 / heart rate).
- We use the widest QT interval.
- QTc = 0.49 in pediatrics / 0.44 in adults.
- **Prolonged QTc causes:**
 - Congenital causes 50% : romano-ward syndrome (AD)/ Jervell and Lange-Nielsen syndrome (AR, associated with sensorineural hearing loss and family history of sudden deaths).
 - Acquired causes 50%: drug-induced (anti-histamines/ erythromycin/ tricyclic anti-depressants/ anti-psychotics).
- **Short QTc causes:** hypercalcemia/ congenital short QT syndrome/ digoxin effect.

✚ General notes:

- Q wave is not present normally in right ventricular leads (V1, V2). If it was present:
 - Wide and deep: ischemia.
 - Deep but not wide: volume overload.
- T wave inversion: 1st change in ischemia.
- ST segment elevation in ischemia.
- ST segment elevation + Q wave = acute infection.
- ST depression causes: ventricular hypertrophy/ hypokalemia/ digoxin effect.

Left to right shunt lesions (acyanotic)

This sheet includes Dr. Iyad Al-ammori slides and notes from the annual lectures. There is no need to refer to slides. Endocardial cushion defect was added from nelson essential. The doctor didn't mention it.



left-to-right shunts (acyanotic lesions)

- Red to blue shunts.
- Portion of fully oxygenated pulmonary venous blood bypassing the systemic flow and going back to the lungs → ineffective pulmonary blood flow.
- It is measured as the ratio of pulmonary to systemic blood flow since the latter is usually constant (compensated for).
- Physiologic effect of the shunt is dependent on three factors: 1) Location of the shunt 2) Size of the defect 3) Relative pulmonary and systemic vascular resistance (or ventricular compliance in case of atrial level shunts).

1) ASD (atrial septal defect)

- Atrial level shunt from left atrium to right atrium.
- Types: ostium secundum (m.c)/ ostium primum (Down syndrome)/ sinus venosus (partial anomalous pulmonary venous return)/ coronary sinus (rare).
- It causes volume load on the right leading to dilation.
- Majority of the shunt occurs during diastole (ventricular filling).
- Cardiac output is well maintained even in large ASD's. Therefore an ASD does not typically cause heart failure.

Assume that the cardiac output is 4 L.
Volume of blood in the right atrium is 4 L.
Assume ASD is large enough to cause another CO to pass to the right atrium, resulting in a total of 8L in the right atrium.
Blood volume in the right ventricle is 8 L → 8 L in pulmonary artery →
Volume of blood returning back to left atrium is 8 L.
The 8 L will be divided into 4 L which is the normal CO, and 4 L to the shunt.
Therefore, the ratio of Q_p/Q_s in this example is 2:1 and the cardiac output is well maintained.

- **Symptoms:**
 - Usually asymptomatic. In some instances there might be dyspnea upon distress. The walls of the pulmonary vasculature are at maximum dilation already because of pulmonary overflow and therefore there's zero compliance and the amount of blood to the lungs cannot be increased.
 - Pulmonary HTN is extremely rare in the young because although there's an increase in pulmonary blood flow, the resistance in the pulmonary vasculature is relatively low.
 - Older individuals may present with arrhythmias like SVT. RA enlargement causes problems with the SA node and dysrhythmias result.
 - Paradoxical emboli can occur as DVT from the lower limb embolizes to the right atrium. Should a transient Right to left shunt occur, the embolus then moves to the left atrium, and then to the systemic circulation where it may lodge in the brain or lower extremities.

- **Physical examination:**
 - Unremarkable in young infants.
 - A systolic ejection murmur might be audible due to overload of the right ventricle.
 - A diastolic murmur is occasionally heard over the tricuspid valve as a result of the increased blood volume passing across the valve.
 - Fixed wide splitting of the second heart sound i.e., unlike physiologic splitting, this split is heard on both inspiration and expiration because of increased volume passing across the pulmonary artery.
 - Right ventricular heave might be palpable if the defect is large enough to cause right ventricular dilation.
- **Diagnostic studies:** Echocardiography is diagnostic/ CXR shows increased pulmonary flow and dilated right atrium, ventricle and pulmonary artery/ ECG.
- **Treatment:** no medical management/ elective surgical or catheterization closure of ASD is advised for moderate and large defects after age of 4 years.

2) VSD (ventricular septal defect)

- Ventricular level shunt (from left ventricle to right ventricle). Pulmonary vascular resistance is less than systemic resistance.
- There are four types of VSD. The most common is the muscular defect but the most clinically significant is the perimembranous (conoverricular), where the defect is under the aortic valve. Inlet type VSD (complete AV canal type) is common in Down syndrome. Sub-pulmonary is conal septal hypoplasia VSD (incidence of aortic valve prolapse).
- It causes Pressure load on the right ventricle causing RVH, and Volume load on the left atrium and ventricle leading to dilation.
- Shunt occurs during Systole (ventricular emptying).
- Cardiac output is well maintained even in large VSD's.

Assume that the CO is 4 L. This 4 L moves from the right atrium, through the tricuspid valve, to the right ventricle. 4 L move from the left ventricle through the VSD to the right ventricle, and so a total of 8 L are now in the right ventricle → lungs → back to the left ventricle. The 8 will be divided in to 4 L passing through into the aorta and another 4 L passing through to the lungs again. The ratio of Q_p/Q_s is quite the same as in an ASD but the effect on the heart is totally different. In what way?

- There's a volume overload in the left ventricle leading to significant left ventricular dilation.
- The right ventricle is receiving both volume and pressure from the left ventricle which in turn leads to right ventricular hypertrophy.

- **Symptoms:**
 - More symptoms than ASD.
 - Amount of blood flow to the lungs is determined by the size of the VSD and the resistance in the pulmonary vasculature. If the pulmonary vascular resistance is high, as in the case of a new born child, the VSD will be asymptomatic.
 - Mod-Large VSD in infants may cause congestive heart failure symptoms after the first month of life.
 - Decreased feeding, diaphoresis and respiratory distress.
 - Failure to thrive.
 - Compensated patients deteriorate rapidly with infection.
- **Examination:**
 - A pan-systolic murmur is appreciated, though in a newborn it might not be auscultated due to high pulmonary vascular resistance. The larger the defect, the less turbulent the flow, and the softer the murmur.
 - A displaced apex beat, due to left ventricular dilatation.
 - A Loud S2 because of pulmonary hypertension (closure of pulmonary valve under high pressure).
 - An S3 gallop brought about by left ventricular dilation (in HF patients).
- **Diagnosis:** ECG/ CXR – displaced left heart border (cardiomegaly) and increased pulmonary vascular markings (increased pulmonary flow)/ echocardiography is diagnostic.
- **Management:**
 - Surgical treatment is the standard treatment for symptomatic VSD's. Done for any patient who can withstand surgery, even if they were only 3 months of age. You do not delay surgery unless there's a reason to wait. It aims to prevent irreversible damage to pulmonary vasculature. Do it before it becomes right to left shunt (irreversible).
 - Treatment of symptomatic patient with heart failure: – Diuresis (Furosemide) – Afterload reduction (captopril) – Inotrope (Digoxin).

3) PDA (patent ductus arteriosus)

- Failure of closure of the ductus arteriosus, which allows the crucial communication between the pulmonary artery and the aorta during fetal life. Typically located just distal to the origin of the left subclavian artery.
- Increased incidence with prematurity. Female to male ratio = 2:1
- Associated with asphyxia, chromosomal anomalies, birth at high altitudes, congenital Rubella, and drugs.
- Everyone is born with a PDA that functionally closes within the first 24 hours of life. Closure is a consequence of increased partial pressure of oxygen as

the newborn takes the first breath, and the effect of cutting the umbilical cord which is the source of prostaglandins that keep the ductus arteriosus patent.

- Prostaglandins: Most important factor in ductal patency – Produced by the placenta and the ductal tissue – Metabolized by the lungs – Ductal tissue is much more sensitive to prostaglandins at earlier gestations.
- Complete “anatomic” closure (fibrosis) usually occurs in the first 2-3 weeks.
- The **pathophysiology** of PDA is very similar to the pathophysiology of VSD in which that it causes increased pulmonary blood flow and venous return; left ventricular dilation (volume overload); and right ventricular hypertrophy (pressure overload). However, unlike VSD it causes - Diastolic hypotension → decreased myocardial coronary perfusion → may worsen congestive heart failure, and a wide pulse pressure with pounding pulses.
- **Presentation:** In premature infants (PVR is low at birth) – Hyperdynamic circulation – Wide pulse pressure – Heart murmur – Increased oxygen requirement due to pulmonary congestion, and increased respiratory distress. In Term infants: Usually asymptomatic in the first few weeks of life (similar to VSD’s) due to high PVR at birth in term infants.
- Assume a patient presents to you complaining of respiratory distress, failure to thrive and diaphoresis with feeding and mobility. There are signs of pulmonary hypertension and cardiomegaly was seen on CXR. On measuring their blood pressure, if it were a 100/60 mmHg then they are likely to have a VSD, but if it were a 100/35 mmHg (wide pulse pressure) the diagnosis is more likely to be a PDA.
- Patients with a PDA do worse than patients with a VSD.
- **Management:**
 - Asymptomatic PDA’s require no treatment before age of 1 year, elective closure can usually be done by catheterization.
 - Symptomatic PDA’s – Symptomatic treatment of CHF (diuresis, inotropic support, and vasodilators) – Avoid lowering PVR (avoid oxygen, alkalosis, NO) – Medical closure (Indomethacin IV, preferably before day 10 of life, Ibuprofen IV has similar effect) – Surgical closure in refractory cases.

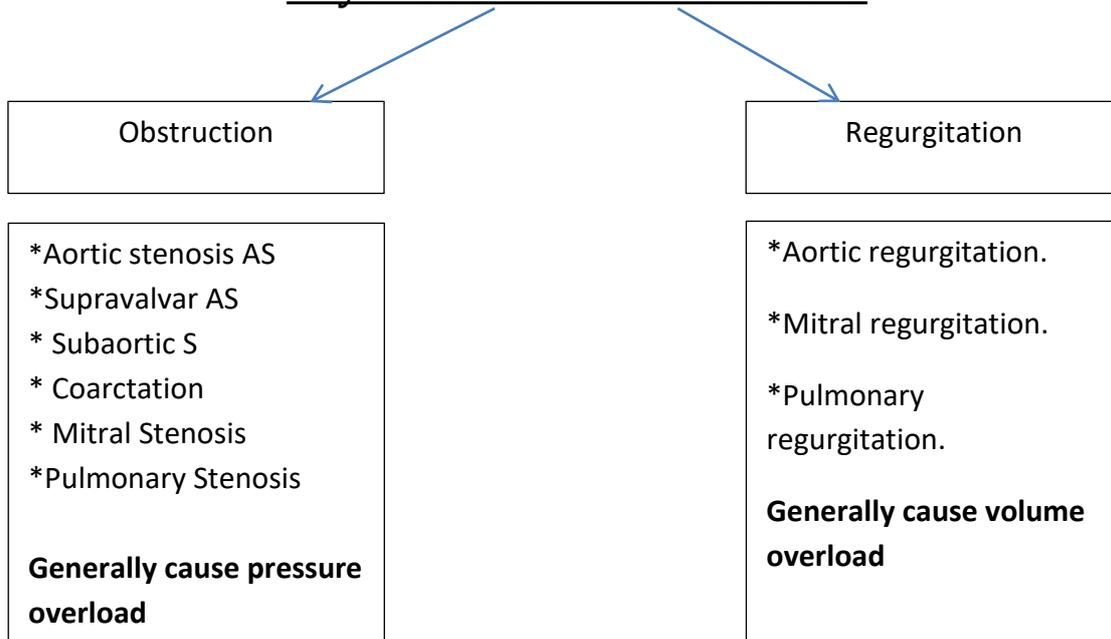
Endocardial cushion defect

- Also referred to as atrioventricular canal defects, may be complete or partial.
- Failure of the septum to fuse with the endocardial cushion results in abnormal atrioventricular valves.

- The complete defect results in a primum ASD, a posterior or inlet VSD, and clefts in the anterior leaflet of the mitral and septal leaflet of the tricuspid valves.
- In addition to left-to-right shunting at both levels, there may be atrioventricular valve insufficiency.
- The symptoms of heart failure usually develop as the pulmonary vascular resistance decreases over the first 6 to 8 weeks of life. The symptoms may be earlier with AV valve insufficiency.
- Pulmonary hypertension resulting from increased pulmonary circulation often develops early.
- The presence of murmurs varies depending on the amount of shunting at both atrial and ventricular levels. If there is a large VSD component, S2 will be single.
- Growth is usually poor.
- Complete endocardial cushion defects are most commonly seen in children with Down syndrome.
- Diagnosis: echocardiography/ cardiomegaly and increased vascularity on X-ray/ An ECG reveals left axis deviation and combined ventricular hypertrophy and may show combined atrial enlargement.
- Treatment: Initial management includes diuretics (\pm digoxin) and afterload reduction for treatment of heart failure. Surgical repair of the defect ultimately is required.

Done by: Farah Ziad & Rafeef Qawasmeh

Acyanotic non-shunt lesions



Coarctation of aorta

- Narrowing of the aortic lumen that causes an obstruction to blood flow.
- Variable degrees of obstruction, anatomic location, and hence clinical manifestations and outcome after treatment.
- High blood pressure in upper part of the body and normal to low blood pressure in the lower part.
- Left ventricular hypertrophy (pressure overload) → Heart failure and pulmonary edema → pulmonary hypertension.
- 3 typical patterns:
 - Infant with congestive heart failure – Catastrophic illness on day 8 - 12 (Shock).
 - Child with a murmur – Subtle signs, pressure gradient, radiofemoral delay on examination.
 - Adolescent – Systolic hypertension, Chest pain, Claudication.
- Treatment: Infants presenting with shock require medical management and immediate surgical treatment. Treatment is surgical coarctectomy, or angioplasty with a balloon or stent placement.

Aortic stenosis

- Lesions result from failure of development of the three leaflets or failure of resorption of tissue around the valve.
- Types: Valvular/ subvalvular/ supravalvular (least common).

- Mild to moderate obstructions cause no symptoms. More severe stenosis results in easy fatigability, exertional chest pain, and syncope. Infants with critical aortic stenosis may present with symptoms of heart failure.
- A systolic ejection murmur is heard at the right second intercostal space along the sternum and radiating into the neck.
- With valvular stenosis, a systolic ejection click often is heard (doesn't change with respiration), and a thrill may be present at the right upper sternal border or in the suprasternal notch. The aortic component of S2 may be decreased in intensity.
- **Diagnosis:**
 - ECG and chest x-ray findings are normal with mild degrees of stenosis.
 - Left ventricular hypertrophy develops with moderate to severe stenosis and is detected on the ECG and chest x-ray.
 - Dilation of the ascending aorta or aortic knob due to an intrinsic aortopathy may be seen on chest X-ray.
 - Echocardiogram (gold standard).
- **Treatment:**
 - Balloon valvuloplasty is usually the first interventional procedure for significant stenosis.
 - Surgical management is necessary when balloon valvuloplasty is unsuccessful or significant valve insufficiency develops.

Pulmonary stenosis

- It can be valvular, subvalvular, or supra-valvular in nature.
- It results from the failure of the development, in early gestation, of the three leaflets of the valve, insufficient resorption of infundibular tissue, or insufficient canalization of the peripheral pulmonary arteries.
- Mild pulmonary stenosis is asymptomatic. Moderate to severe stenosis results in exertional dyspnea and easy fatigability. Newborns with severe stenosis may be more symptomatic and even cyanotic.
- Systolic ejection murmur at the second left intercostal space which radiates to the back.
- A thrill may be present. S2 may be widely split with a quiet pulmonary component.
- An impulse at the lower left sternal border results from right ventricular hypertrophy.
- Valvular stenosis may result in a click that varies with respiration.

- **Diagnosis:**
 - ECG and chest x-ray findings are normal in mild stenosis.
 - Moderate to severe stenosis results in right axis deviation and right ventricular hypertrophy.
 - The heart size is usually normal on chest x-ray, although dilation of the main pulmonary artery may be seen.
 - Echocardiography provides assessment of the site of stenosis, degree of hypertrophy, and valve morphology, as well as an estimate of the pressure gradient.
- **Treatment:**
 - Balloon valvuloplasty is usually successful in reducing the gradient to acceptable levels for more significant or symptomatic stenosis. It is more successful than aortic balloon valvuloplasty.
 - Surgical repair is required if balloon valvuloplasty is unsuccessful or when subvalvular (muscular) stenosis is present.

Tricuspid regurgitation (insufficiency)

- Usually associated with Ebstein anomaly.
- Often with right ventricular dysfunction.
- With perinatal asphyxia in neonate (ischemia of papillary muscles).

Mitral regurgitation (insufficiency)

- Usually with other lesions (ASD, VSD, dilated cardiomyopathy).
- In the absence of other congenital heart disease, endocarditis or rheumatic fever should be suspected in a patient with isolated severe mitral insufficiency.
- In isolated mitral insufficiency, the mitral valve annulus is usually dilated, the chordae tendineae are short and may insert anomalously, and the valve leaflets are deformed.
- The left atrium enlarges as a result of the regurgitant flow, and the left ventricle becomes hypertrophied and dilated → increased pulmonary venous pressure → pulmonary hypertension.
- High pitched holosystolic murmur at apex.
- In severe cases: respiratory infections, fatigue, pulmonary edema and CHF.
- ECG: bifid P waves/ left ventricular hypertrophy.
- Chest X-ray: prominent left ventricle/ increased left atrial size.
- Echocardiography is the gold standard.
- Treatment: mitral valvuloplasty.

This sheet was written from the slides, Kaplan and Nelson

Cyanotic heart diseases

This sheet was written from Dr. Iyad Al-ammouri slides and lecture notes in addition to some notes from the old sheet. No need to refer to slides.

Cyanosis:

Cyanosis in children happens when there is clinically apparent amount of desaturated hemoglobin. Usually occurs with 3-4 grams/ dL of reduced hemoglobin. This usually corresponds to oxygen saturation of 70-80%. Therefore mild desaturation may clinically be missed.

Cyanosis is easier to be shown on polycythemia patient rather than anemic (easier manifestations of desaturation).

General causes of cyanosis:

1. Pulmonary causes (the most common): airway disease or intrapulmonary shunting.
2. Cardiac causes: only intra-cardiac shunting.
3. Others.

Hyperoxia test: Administration of 100% O₂ for 15 minutes to measure arterial PO₂. If PO₂ <15 it is cardiac cyanosis. If it is >250 then it is pulmonary cyanosis. This test is rarely used nowadays.

Cyanotic heart diseases (5T's):

1. TOF
2. Transposition of great vessels.
3. Truncus arteriosus.
4. Tricuspid atresia.
5. Total anomalous pulmonary venous return.

Mechanisms of cardiac cyanosis:

1. Right to left shunt: Tetralogy of Fallot (TOF)
2. Mixing: tricuspid atresia/ truncus arteriosus/ single ventricle.
3. Recirculation: transposition of great vessels (TGA).

1) Tetralogy of fallot (TOF)

As the name implies, it consists of 4 malformations:

1. Right ventricular outlet obstruction.
2. VSD

3. Overriding aorta.
4. Right ventricular hypertrophy.

- ☒ TOF is the most common cyanotic heart disease and the 3rd most common congenital heart disease (VSD is the most common THEN ASD).
- ☒ In the extreme form there is complete pulmonary atresia.
- ☒ Cardiac output is normal.
- ☒ The more right to left shunt → less saturation.

TOF is a dynamic disease with hyper-cyanotic spells:

- ☒ Pt in severe cyanosis is almost impending death manner; cyanosis is profound which induces agitation and tachycardia ending up with LOC or death.
- ☒ Hyper-cyanotic spell usually happens due to increased right to left shunt and thus less saturation (more blue blood to systemic circulation).
- ☒ Increased shunt is caused by increased pulmonary vascular resistance or increased right ventricular outlet obstruction. The latter is caused by impaired right ventricular filling and advancing age.
- ☒ Hyper-cyanotic spell usually happens in early morning while patient is hungry and hypovolemic leading to tachycardia which in turn leads impaired right ventricular filling and thus more obstruction → more blood to left ventricle via VSD → more cyanosis → more agitation and so on till LOC.
- ☒ Treatment: oxygen, knee chest position (we try to increase systemic vascular resistance by this position pushing blood toward lungs). Fluid management for hypovolemia. Sedation (Morphine) to decrease agitation.
- ☒ Children with this anomaly learned by themselves that squatting is helpful. It increases oxygen saturations in which that angulation and kinking of femoral arteries increases SVR and thus decreasing the R->L shunt.

Clinical features:

- ☒ Variability of presentation is related to degree of RVOT obstruction.
- ☒ Consistency of symptoms is related to fixed vs. dynamic obstruction.
- ☒ Cyanosis typically appears between 6 weeks and 6 months in the unrepaired infant.
- ☒ May be present at rest or only with agitation/exercise.
- ☒ Persistent cyanosis and clubbing if not repaired.
- ☒ Hyper-cyanotic spells.

Chest X-ray (boot shape heart)

- ☒ Normal heart size.
- ☒ Uprturned apex.
- ☒ Concave upper left heart border.

- ☒ Normal or decreased pulmonary vascular markings.

Management: surgical (VSD closure Relief of RVOT obstruction).

2) Transposition of great arteries (TGA)

- ☒ Aorta originating from the right ventricle and pulmonary artery originating from the left ventricle.
- ☒ It is the 2nd most common cyanotic heart disease after TOF.
- ☒ It usually presents in 1st day of life with profound cyanosis.
- ☒ More common in boys.
- ☒ Survival is dependent on the presence of mixing between the pulmonary and systemic circulation. ASD is essential for survival.
- ☒ CXR - egg on string appearance/ Narrow mediastinum.
- ☒ Management:
 - PGE-1 (prostaglandins): Maintain ductus arteriosus patency → increase the effective pulmonary blood flow → increase the left atrial pressure → enhance the left to right shunt at the atrial level.
 - Balloon atrial septostomy (to dilate the patent foramen ovale by a balloon) Life-saving procedure in the presence of inadequate ASD.

3) Truncus arteriosus

- ☒ The presence of a common trunk that supply the systemic, pulmonary and coronary circulation.
- ☒ Complete mixing of blood, HF at the age of 1-2 month due to high volume of blood goes to the lungs.
- ☒ Almost always associated with VSD.
- ☒ Degree of cyanosis is mild and may not be evident clinically until late stage with pulmonary vascular disease.
- ☒ Presenting feature is congestive heart failure (tachypnea, hepatomegaly).

4) Tricuspid atresia

- ☒ Complete absence of communication between the right atrium and right ventricle.
- ☒ Patient must have ASD to survive.
- ☒ Usually associated with VSD. The pulmonary blood flow is dependent on the size of the VSD; it can be increased or decreased causing variable presenting symptoms. If there is no VSD, the pulmonary blood flow is dependent on the PDA.

- ☒ Cardiomegaly (not in others).
- ☒ Surgical management: Single ventricle palliation (done in stages: the systemic veins are connected to the pulmonary artery directly to bypass the right ventricle).

5) **Total anomalous pulmonary venous return (TAPVR)**

- ☒ 3 types:
 - Supracardiac (supradiaphragmatic): pulmonary veins open into superior venacava → right atrium.
 - Infracardiac (infradiaphragmatic): pulmonary veins open into inferior vena cava.
 - Intracardiac.
- ☒ The presence of ASD is essential for survival to supply blood to the left atrium and ventricle.
- ☒ Presentation is usually by cyanosis and mild respiratory distress. It is late (at 2 years of age).
- ☒ CXR: snowman appearance in supracardiac type. No cardiomegaly here, it is just dilatation of SVC. In the intracardiac type it shows normal heart size with pulmonary edema (due to obstruction of pulmonary veins at the level of esophageal hiatus where they cross to drain into the heart).

Kawasaki disease

It is an acute vasculitis of unknown etiology that is characterized by multisystem involvement and inflammation of all blood vessels, but mostly medium-sized arteries; especially coronary, with resulting aneurysm formation.

It is the leading cause of acquired heart diseases in USA and Japan. 80% of cases occur before age of 5 years. It is more common in boys.

The cause of KD remains unknown, but certain epidemiologic and clinical features support an infectious origin. These features include the young age group affected, epidemics with wave-like geographic spread of illness, the self-limited nature of the acute febrile illness, and the clinical features.

A genetic role in the pathogenesis of KD seems likely, as evidenced by the higher risk of KD in Asian children regardless of country of residence, and in siblings and children of individuals with a history of KD.

Pathology:

A 3-phase process to the arteriopathy of KD has been described.

1. The 1st phase is a neutrophilic necrotizing arteritis occurring in the 1st 2 weeks of illness that begins in the endothelium and moves through the coronary wall. Saccular aneurysms may form from this arteritis.
2. The second phase is a subacute/chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils, which may last from weeks to years and results in fusiform aneurysms.
3. The vessels affected by the subacute/chronic vasculitis then develop smooth muscle cell myofibroblasts, which cause progressive stenosis. Thrombi may form in the lumen and obstruct blood flow.

Criteria of diagnosis:

Fever for \geq 5 days not improved with ibuprofen or acetaminophen plus 4 of following 5 criteria:

1. Bilateral bulbar conjunctivitis without exudate.
2. Intraoral erythema, strawberry tongue, dry and cracked lips.
3. Erythema and swelling of hands and feet; desquamation of fingertips 1-3 weeks after onset.
4. Various forms of rash; but not vesicular.
5. Non-suppurative cervical lymphadenitis; asymmetric, >1.5 cm.

Other clinical manifestations:

Irritability/ aseptic meningitis/ diarrhea/ hepatitis/ hydrops of gallbladder/ otitis media/ arthritis/ urethritis with sterile pyuria.

Cardiac involvement:

- It is the most important manifestation of KD.
- Myocarditis occurs in most patients with acute KD and manifests as tachycardia disproportionate to fever, along with diminished left ventricular systolic function.
- Occasionally, patients with KD present in cardiogenic shock (KD shock syndrome), with markedly diminished left ventricular function.
- Pericarditis with a small pericardial effusion can also occur during the acute illness.
- Mitral regurgitation of at least mild severity is evident on echocardiography in 10-25% of patients at presentation but diminishes over time, except among rare patients with coronary aneurysms and ischemic heart disease.
- Coronary aneurysm develops in up to 25% of untreated patients in the 2nd to 3rd week of illness.
- Giant coronary artery aneurysms (classic definition of >8 mm internal diameter) pose the greatest risk for rupture, thrombosis or stenosis, and myocardial infarction.
- Axillary, popliteal, iliac, or other arteries may also become dilated, which manifest as a localized pulsating mass.

Lab findings:

- Increased ESR and CRP.
- Normal or increased WBC (predominance of neutrophils and immature forms).
- Normocytic normochromic anemia.
- The platelet count is generally normal in the 1st wk of illness and rapidly increases by the 2nd to 3rd wk of illness, sometimes exceeding 1,000,000/mm³.
- Sterile pyuria.
- Increased ALT, AST.
- Hyperbilirubinemia.
- CSF pleocytosis.

Echocardiography:

- ☒ Two-dimensional echocardiography is the most useful test to monitor for development of coronary artery aneurysm.
- ☒ It should be performed at diagnosis and again after 2-3 weeks of illness. If the results are normal, a repeat study should be performed 6-8 weeks after onset of illness.
- ☒ More frequent echocardiograms and, potentially, coronary angiography are indicated for patients who develop coronary artery abnormalities.

Differential diagnosis:

- ☒ Incomplete (atypical) KD, which occurs more commonly in infants, is diagnosed when fever is present for at least 5 days even if only two or three clinical criteria are present, particularly in the presence of coronary artery aneurysms.
- ☒ Adenovirus, measles, and scarlet fever lead the list of common childhood infections that mimic KD.
- ☒ Less common infections such as Rocky Mountain spotted fever and leptospirosis are occasionally confused with KD.
- ☒ Toxic shock syndrome.
- ☒ Drug hypersensitivity reactions, including Stevens Johnson syndrome, share some characteristics with KD.
- ☒ Systemic onset juvenile idiopathic arthritis.
- ☒ Polyarteritis nodosa/ Behçet syndrome.

Treatment:

- ☒ Patients with acute KD should be treated with 2 g/kg of IVIG and high dose aspirin (anti-inflammatory dose), (80-100 mg/kg/day divided q 6h) within 10 days of disease onset and ideally as soon as possible after diagnosis.
- ☒ Once the fever resolves, aspirin is reduced to antithrombotic doses (3 to 5 mg/kg/day as a single dose) and given through the subacute and convalescent phases, usually for 6 to 8 weeks.
- ☒ Corticosteroids or infliximab are rarely used in KD, as opposed to other vasculitides, but may have a role during the acute phase if active carditis is apparent or for children with persistent fever after two doses of IVIG.
- ☒ Patients undergoing long-term aspirin therapy should receive annual influenza vaccination to reduce the risk of Reye syndrome.
- ☒ IVIG-resistant KD occurs in approximately 15% of patients and is defined by persistent or recrudescing fever 36 hr after completion of the initial IVIG infusion. They are at increased risk for CAA. Recommendation is to give a

second dose of IVIG. If no response to second IVIG dose, give pulse steroid therapy.

Complications and prognosis:

- ☒ No evidence of long term cardiovascular sequelae in those who don't have coronary abnormalities within 2 months of onset.
- ☒ Coronary artery thrombosis/ Peripheral artery aneurysm/ Coronary artery aneurysms/ Myocardial infarction/ Myopericarditis/ Heart failure/ Hydrops of gallbladder/ Aseptic meningitis.

Rheumatic fever

It is the most common form of acquired heart diseases worldwide. It is an important preventable cause.

It is most common in children 5 to 15 years of age.

It is due to an immunologic reaction that is a delayed sequela of group A beta-hemolytic streptococcal infections of the pharynx. A family history of rheumatic fever and lower socioeconomic status are additional factors.

Cell wall of group A streptococcus contains a highly antigenic protein (M protein). Anti-M proteins may cross react with cardiac and smooth muscle myosin inducing cytokine release and tissue destruction.

Criteria of diagnosis: Jones criteria

The presence of either two major criteria or one major and two minor criteria, along with evidence of an antecedent streptococcal infection, confirm the diagnosis. The infection often precedes the presentation of rheumatic fever by 2 to 6 weeks. Streptococcal antibody tests, such as the antistreptolysin O titer and anti-DNase, are the most reliable laboratory evidence of prior infection.

MAJOR criteria	MINOR criteria
Carditis. Polyarthrititis. Erythema marginatum. Chorea (Sydenham). Subcutaneous nodule.	Fever. Arthralgia (in the absence of arthritis). Increased ESR, CRP. Prolonged PR interval. Previous rheumatic fever.

- ☒ **Arthritis:** very painful, migratory, involving large joints, nondestructive.
- ☒ **Carditis:** presents as congestive heart failure, new murmur friction rub of pericarditis.
- ☒ **Subcutaneous nodule:** non-tender nodules on the extensor surfaces of joints (very infrequent).
- ☒ **Erythema marginatum:** Long lasting skin rash on the trunk or limbs.
- ☒ **Chorea:** can be very late in the disease. Sydenham chorea: Uncommon; manifests long after infection has resolved; more common in females; antineuronal antibody positive.
- ☒ **Sydenham chorea alone is sufficient for diagnosis.**

Treatment:

- Anti-inflammatory therapy with salicylates, and bed rest.
- Oral penicillin or erythromycin for 10 days; then prophylaxis.
- Long-term penicillin prophylaxis, preferably with intramuscular benzathine penicillin G, 1.2 million U every 28 days, is required. Oral regimens for prophylaxis generally are not as effective.
- Aspirin in carditis/ arthritis without CHF. In CHF, give prednisone for 2-3 weeks, then taper for 6 weeks.
- Digoxin/ diuretics/ salt restriction.
- If chorea is isolated, give phenobarbital.

Complications:

- Most have no residual heart disease.
- Valvular heart disease is the most important.

Prevention:

- Continuous antibiotics prophylaxis.
- Single IM benzathine penicillin G every 4 weeks.

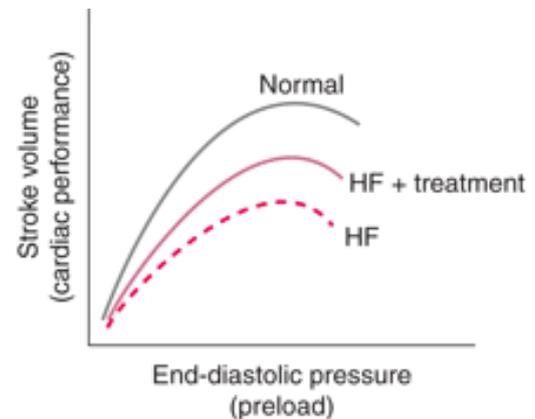
The previous two sheets (KD and rheumatic fever) were written from Kaplan, Nelson textbook and Nelson essentials, in addition to some notes from the old lecture.

Heart failure

Heart failure occurs when the heart cannot deliver adequate cardiac output to meet the metabolic needs of the body.

The Frank-Starling principle

As ventricular end-diastolic volume increases, a healthy heart increases cardiac output until a maximum is reached (critical point) and cardiac output can no longer be augmented. Alterations in the contractile state of the muscle lower the relative position of the curve, but retain the relationship of fiber length to muscle work. Adding an inotropic agent (digoxin) shifts the curve from the one designated "HF" in picture to the one designated "HF + treatment".



Mechanisms of heart failure:

1. Change in myocardial contractility that results in low cardiac output (dilated cardiomyopathy, myocarditis).
2. Increased afterload (pressure overload, such as with aortic stenosis, pulmonary stenosis, or coarctation of the aorta).
3. Increased preload (volume overload, such as in ventricular septal defect (VSD), patent ductus arteriosus (PDA), or valvular insufficiency). **Volume overload is the most common cause of heart failure in children.**

Differential diagnosis according to age:

- ☒ In the first weeks of life, excessive afterload being placed on the myocardium is most common.
- ☒ Heart failure presenting around 2 months of age is usually due to increasing left-to-right shunts that become apparent as the pulmonary vascular resistance decreases.
- ☒ Acquired heart disease, such as myocarditis and cardiomyopathy, can present at any age.

Etiology of heart failure according to age				
Fetal	Premature neonate	Full-term neonate	Infant- toddler	Child- adolescent
*Severe anemia. *Supraventricular tachycardia. *Ventricular tachycardia. *Complete heart block. *Severe Ebstein anomaly or other severe right-sided lesions. *Myocarditis	*Fluid overload *PDA *VSD *Cor pulmonale (bronchopulmonary dysplasia) *Hypertension *Myocarditis *Genetic cardiomyopathy	*Asphyxial cardiomyopathy *Arteriovenous malformation (vein of Galen, hepatic). *Left-sided obstructive lesion. *Large mixing cardiac defects *Myocarditis *Genetic cardiomyopathy	*Left-to-right cardiac shunts. *Hemangioma *Anomalous left coronary artery *Genetic or metabolic cardiomyopathy *Acute hypertension (HUS) *Supraventricular tachycardia *Kawasaki disease *Myocarditis	*Rheumatic fever *Acute hypertension *Myocarditis *Thyrotoxicosis *Hemochromatosis-hemosiderosis *Cancer therapy *Sickle cell anemia *Endocarditis *Cor pulmonale (cystic fibrosis) *Genetic or metabolic cardiomyopathy

High-output heart failure

In some cases of heart failure, cardiac output is normal or increased, yet because of decreased systemic oxygen content (secondary to anemia) or increased oxygen demands (secondary to hyperventilation, hyperthyroidism, or hypermetabolism), an inadequate amount of oxygen is delivered to meet the body's needs. This condition, high-output failure, results in the development of signs and symptoms of heart failure when there is no basic abnormality in myocardial function and cardiac output is greater than normal.

Clinical manifestations

- ☒ Heart failure presents in infants as poor feeding, failure to thrive, tachypnea, and diaphoresis with feeding.
- ☒ Older children may present with shortness of breath, easy fatigability, and edema.
- ☒ The physical examination findings depend on whether pulmonary venous congestion, systemic venous congestion, or both are present. Tachycardia, a gallop rhythm, and thready pulses may be present with either cause.
- ☒ If left-sided failure is predominant, tachypnea, orthopnea, wheezing, and pulmonary edema are seen.
- ☒ Hepatomegaly, edema, and distended neck veins are signs of right-sided failure.

Diagnosis

- ☒ **X-ray of the chest** show cardiac enlargement. Pulmonary vascularity is variable and depends on the cause of the heart failure. The absence of cardiomegaly on a chest x-ray usually rules out the diagnosis.
- ☒ **ECG:** Chamber hypertrophy noted by electrocardiography may be helpful in assessing the cause of heart failure but does not establish the diagnosis. It is the best tool for evaluating rhythm disorders as a potential cause of heart failure, especially tachyarrhythmias.
- ☒ **Echocardiography** is the standard technique for assessing ventricular function. It can assess the heart chamber sizes, measure myocardial function, and diagnose congenital heart defects when present. The most commonly used parameter in children is fractional shortening unlike adults in which ejection fraction is the most commonly used. But in children with right ventricular enlargement or other cardiac pathology resulting in flattening of the interventricular septum, ejection fraction is used because fractional shortening measured in the standard echocardiographic short-axis view will not be accurate.
- ☒ **Doppler studies.**
- ☒ **Magnetic resonance angiography** is very useful in quantifying left and right ventricular function, volume and mass as well as coronary artery anatomy.
- ☒ **Serum B-type natriuretic peptide**, a cardiac neurohormone released in response to increased ventricular wall tension, may be elevated in patients with heart failure as a result of systolic dysfunction (cardiomyopathy), as well as in children with volume overload.

Treatment:

- ☒ Initial treatment is directed at improving myocardial function and optimizing preload and afterload.
- ☒ Long-term therapy usually consists of diuretics and afterload reduction is added.
- ☒ Long-term therapy with β -blockers also may be beneficial, although this remains somewhat controversial in pediatric patients.
- ☒ Spironolactone is usually added to the medical regimen because of its effect on cardiac remodeling.
- ☒ Rest → Reduces cardiac output.
- ☒ Oxygen → Improves oxygenation in presence of pulmonary edema.
- ☒ Sodium, fluid restrictions → Decrease vascular congestion and preload.
- ☒ Diuresis (Furosemide) → Salt excretion by way of ascending loop of Henle; reduces preload; afterload reduced with control of hypertension; may also cause venodilation.

- ☒ Combination of distal tubule and loop diuretics → Greater sodium excretion.
- ☒ Inotropic agents:
 - Digitalis → Inhibits membrane Na⁺/ K⁺-ATPase and increases intracellular Ca²⁺, improves cardiac contractility, increases myocardial oxygen consumption.
 - Dopamine → Releases myocardial norepinephrine plus direct effect on β-receptor, may increase systemic blood pressure.
 - Dobutamine → β₁-Receptor agent; often combined with dopamine.
 - Amrinone/ milrinone → Nonsympathomimetic, noncardiac glycosides with inotropic effects; may cause vasodilation.
- ☒ Afterload reduction:
 - Hydralazine → arteriolar vasodilator.
 - Nitroprusside → Arterial and venous relaxation; venodilation reduces preload.
 - Captopril/enalapril → Inhibition of angiotensin-converting enzyme; reduces angiotensin II production.
- ☒ Mechanical counterpulsation improves coronary flow.
- ☒ Transplantation.
- ☒ Extracorporeal membrane oxygenation bypasses heart.

This sheet was written from nelson textbook and nelson essentials.

Dysrhythmias

Cardiac dysrhythmias or abnormal heart rhythms are uncommon in pediatrics but may be caused by infection and inflammation, structural lesions, metabolic abnormalities, and intrinsic conduction abnormalities.

Sinus arrhythmia is a common finding in children and represents a normal variation in the heart rate associated with breathing.

Atrial dysrhythmias	Ventricular dysrhythmias
<p>Wandering atrial pacemaker: a change in the morphology of the P waves with variable PR interval and normal QRS complex. This is a benign finding.</p> <p>Premature atrial contractions: (premature P wave). The premature atrial activity may be blocked (no QRS following it), conducted normally (normal QRS present), or conducted aberrantly (a widened, altered QRS complex). They are usually benign.</p> <p>Atrial flutter and atrial fibrillation are uncommon in pediatrics and usually present after surgical repair of complex congenital heart disease. They may also be seen with myocarditis or in association with drug toxicity.</p> <p>Supraventricular tachycardia (SVT) is the most common symptomatic dysrhythmia in pediatric patients. The rhythm has a rapid, regular rate with a narrow QRS complex. The tachycardia has an abrupt onset and termination. In a child with a structurally normal heart, most episodes are relatively asymptomatic other than a pounding heartbeat. If there is structural heart disease or the episode is prolonged (>12 hours), there may be alteration in the cardiac output and development of symptoms of heart failure.</p>	<p>Premature ventricular contractions (PVCs) are less common than premature atrial contractions in infancy but more common in older children and adolescents. The premature beat is not preceded by a P wave and the QRS complex is wide and bizarre. The PVCs are usually benign. Any deviation from the presentation (history of syncope or a family history of sudden death) requires further investigation and possibly treatment.</p> <p>Ventricular tachycardia, defined as three or more consecutive PVCs, is also relatively rare. Although there are multiple causes, it is usually a sign of serious cardiac dysfunction or disease. Rapid-rate ventricular tachycardia results in decreased cardiac output and cardiovascular instability. Treatment in symptomatic patients is synchronized cardioversion. Medical management with lidocaine or amiodarone may be appropriate in a conscious asymptomatic patient. Complete evaluation of the etiologic picture is necessary, including electrophysiologic study.</p>

Heart block			
1st degree	2nd degree	3rd degree	complete
<p>Prolonged PR interval.</p> <p>It is asymptomatic and, when present in otherwise normal children, requires no evaluation or treatment.</p>	<p>It is when some, but not all, of the P waves are followed by a QRS complex.</p> <p>Mobitz type I (Wenckebach) is characterized by a progressive prolongation of the PR interval until a QRS complex is dropped. It is often seen during sleep, usually does not progress to other forms of heart block, and does not require further evaluation or treatment.</p> <p>Mobitz type II is present when the PR interval does not change, but a QRS is intermittently dropped. This form may progress to complete heart block and may require pacemaker placement.</p>	<p>Congenital or acquired.</p> <p>It is present when there is no relationship between atrial and ventricular activity.</p> <p>The ventricular rate is much slower than the atrial rate.</p>	<p>Congenital form is associated with maternal collagen vascular disease (such as SLE or Sjögren syndrome) or congenital heart disease.</p> <p>The acquired form most often occurs after cardiac surgery but may be secondary to infection, inflammation, or drugs.</p>

Treatment:

- ☒ Most atrial dysrhythmias require no intervention.
- ☒ Acute treatment of SVT in infants usually consists of vagal maneuvers, such as application of cold (ice bag) to the face. IV adenosine usually converts the dysrhythmia.
- ☒ In patients with cardiovascular compromise at the time of presentation, synchronized cardioversion is indicated using 1 to 2 J/kg.
- ☒ Ongoing pharmacologic management with either digoxin or a β -blocker is usually the first choice. However, digoxin is contraindicated in patients with Wolff-Parkinson-White syndrome.
- ☒ In patients who are symptomatic or those not wanting to take daily medications, radiofrequency ablation may be performed.

This sheet was written from nelson essential

Cardiomyopathies

A cardiomyopathy is an intrinsic disease of the heart muscle and is not associated with other forms of heart disease.

There are three types of cardiomyopathy based on anatomic and functional features:

1. Dilated cardiomyopathies:

- The most common.
- They are often idiopathic, but may be due to infection (echovirus or Coxsackie B virus) or be postinfectious, familial, or secondary to systemic disease or to cardiotoxic drugs.
- Manifestations: enlargement of the left ventricle only or of both ventricles/ Myocardial contractility is variably decreased/ signs and symptoms of inadequate cardiac output and heart failure.
- Examination: Tachypnea and tachycardia/ Peripheral pulses are often weak because of a narrow pulse pressure/ Rales may be audible on auscultation/ the heart sounds may be muffled, and an S3 is often present.
- Concurrent infectious illness may result in circulatory collapse and shock.
- Imaging studies: X-ray (cardiomegaly)/ ECG: nonspecific ST-T wave changes and left ventricular hypertrophy. ECG evidence of right ventricular hypertrophy is present in 25%/ Echocardiography: left atrial and ventricular dilation, a decreased shortening fraction, and globally depressed contractility.

2. Hypertrophic cardiomyopathies

- They are usually familial with AD inheritance, but may occur sporadically.
- It is initially difficult to diagnose. Infants, but not older children, frequently present with signs of heart failure.
- Sudden death may be the initial presentation in older children.
- Dyspnea, fatigue, chest pain, syncope or near-syncope, and palpitations may be present.
- A murmur is heard in more than 50% of children referred after identification of an affected family member.
- Imaging studies: X-ray (cardiomegaly)/ ECG: it is universally abnormal, but changes are nonspecific. Primary hypertrophic cardiomyopathy is associated with a prolonged QT interval/

echocardiography: Asymmetrical septal hypertrophy and left ventricular outflow tract obstruction/

3. **Restrictive cardiomyopathies**

- Rare.
- They may be idiopathic or associated with systemic disease.
- Presenting symptoms usually include dyspnea exacerbated by a respiratory illness, syncope, hepatomegaly, and an S4 heart sound on examination.
- Imaging studies: X-ray (cardiomegaly)/ ECG: atrial enlargement/ echocardiography: massive atrial dilation.

Endomyocardial biopsy specimens, obtained while the patient is hemodynamically stable, identify histologic type and allow tests for mitochondrial or infiltrative diseases.

Treatment:

Supportive therapy, including diuretics, inotropic medications, and afterload reduction, is provided for all three types of cardiomyopathy. If a specific etiology can be identified, treatment is directed at the etiology. Symptomatic therapy with close monitoring and follow-up is crucial. Because of the high mortality rate associated with all forms of cardiomyopathy, cardiac transplantation must be considered.

This sheet was written from nelson essential

Infective endocarditis

It is mostly caused by streptococcus viridians (alpha hemolytic) and staphylococcus aureus. Staphylococcus endocarditis is more common in those without underlying heart disease. Streptococcus viridians is more common in those with underlying heart disease or after dental procedures.

Other organisms:

- ☒ Group D streptococci: associated with large bowel or genitourinary manipulation.
- ☒ Fungi: after open heart surgery.
- ☒ Pseudomonas aeruginosa and Serratia marcescens: intravenous drug users.
- ☒ Coagulase negative staphylococcus: indwelling intravenous catheters.

Risk factors:

- ☒ Highest risk with prosthetic valve and uncorrected cyanotic heart lesions.
- ☒ Surgical or dental procedures (high risk with poor dental hygiene).

Clinical presentation:

- ☒ Prolonged intermittent fever, weight loss, fatigue, myalgia, arthralgia, headache, nausea and vomiting.
- ☒ New or changing heart murmur.
- ☒ Splenomegaly, petechiae, embolic stroke, CNS abscess and hemorrhage, and mycotic aneurysm (more with staphylococcus).
- ☒ Skin findings are rare and late; represent vasculitis from circulating Ag-Ab complexes; if present, are highly suggestive: osler nodes/ Janeway lesions/ splinter hemorrhage/ roth spots.

Duke criteria for diagnosis (2 major or 1 major + 3 minor or 5 minor)

Major criteria	Minor criteria
Positive blood culture (2 separate for usual pathogens; at least 2 for less common).	Predisposing conditions/ fever/ emboli or vascular signs/ single positive blood culture// echocardiographic signs not meeting the criteria.
Evidence on echocardiogram (intracardiac or valve lesion, abscess, prosthetic regurgitant flow, partial dehiscence of prosthetic valve, new valvular regurgitant flow).	Immune complex disease (GN, arthritis, positive RF, osler node, roth spots).

Complications

- Heart failure from aortic or mitral lesions (most common).
- Systemic or pulmonary emboli.
- Myocardial abscess.
- Myocarditis, valve obstruction.
- Heart block.
- Meningitis, osteomyelitis, arthritis, renal abscess.
- Immune complex mediated glomerulonephritis.

Treatment:

- Organism specific for 4 – 6 weeks.
- Digitalis, diuretics and salt restriction for heart failure.
- Surgery indications: severe aortic or mitral involvement with intractable failure, failure of blood culture to clear, recurrent emboli, abscess, increasing size of vegetations with worsening regurgitation.
- Prophylaxis (drug of choice is amoxicillin).

This sheet was written from Kaplan

The END
Rafeef Qawasmeh

Respiratory

Asthma

This brief sheet includes seminar notes from Dr. Muna Khater. You can find more details about asthma in immunology and allergy section in this dossier.

- It is a chronic inflammatory airway disease of the small-to-medium sized bronchioles, characterized by hyper-responsiveness of smooth muscles.
- Increased mucus production/ increased smooth muscle contractions/ hyper-responsiveness.

- **Extrinsic asthma:**
 - Atopic/ allergic.
 - Elevated levels of IgE.
 - Triggers (contain protein):
 - ✓ Food (milk, wheat, eggs, fish and nuts).
 - ✓ Pollens.
 - ✓ Spores of fungi.
 - ✓ Dust mites.
 - ✓ Cat dander/ dogs/ birds/ rabbits/ hamsters.

- **Intrinsic asthma:**
 - Intrinsic triggers: viral and bacterial.
 - Extrinsic triggers (don't contain protein): dust/ perfumes/ pollution/ B-blockers/ aspirin.

- **Presentation:**
 - Difficult to breathe out (prolonged expiration).
 - Wheezes.
 - Cough.
 - Dyspnea/ tachypnea.
 - Sigh breath during sleep.

- Recurrent viral infection is the most common cause of asthma in children.
- The most common trigger of asthma through intrinsic pathway is cold air followed by exercise.
- Flowers elicit asthma reaction through mold spores.

- **How to diagnose asthma?**
 - Methacholine challenge test (gold standard): very invasive, we don't do it.
 - Spirometry (best choice): if there is no attack we induce it by exercise.
 - X-ray: only for exclusion of other diseases.

- In children who can't do spirometry: trial of medical therapy and bronchodilators.
- **Treatment (acute attack):**
 - Short acting B-agonist bronchodilator.
 - Theophylline: anti-inflammatory and bronchodilator/ not used anymore because of narrow therapeutic index.
 - Oxygen (if hypoxic).
 - Anti-inflammatory steroids: start to work 4 hours later/ no role in acute attack.
- **For control:**
 - Inhaled corticosteroids.
 - Nedocromil sodium.
 - Leukotrienes.

Rafeef Qawasmeh

Cystic fibrosis (CF)

Etiology

- It is an autosomal recessive disorder. It is a disease of childhood, adolescence and adults.
- It is the most common life-limiting recessive genetic disease in whites.
- Cystic fibrosis patients are immunocompetent.
- The gene for Cystic fibrosis (CF) located on the **long arm of chromosome 7** encodes for a polypeptide, the **Cystic fibrosis transmembrane regulator (CFTR)**.
- CFTR :
 - It is a chloride channel that is located on the apical surface of the epithelial cells.
 - It is essential for the movement of salt and water across cell membranes.
 - It maintains appropriate composition of secretions especially in airways, liver & Pancreas.
 - The most common mutation is a deletion of 3 base pairs resulting in the absence of Phenylalanine at the 508 position (**Δ F508**).
 - More than 1500 mutations of the CFTR gene have been identified.
 - Abnormal CFTR alters Cl^- conductance in sweat glands and this is responsible for the elevated sweat Cl^- in CF patients.
 - The abnormal airway secretions make airways more prone to colonization with bacteria.
- 5 classes of mutations:
 - Class I: CFTR production is stopped early and protein production becomes defective. Class 1 patients have no functioning CFTR chloride channels.
 - Class II: The CFTR is not processed properly and gets destroyed within the cell. Little or no CFTR reaches the cell surface. The most common class 2 mutation is F508del.
 - Class III: Even though the CFTR reaches cell surface it does not work. It does not open properly to transport chloride.
 - Class IV: CFTR reaches the apical surface but its function is poor. The conduction of chloride through the channel is defective.
 - Class V: There is decreased production of CFTR. The CFTR that reaches the cell surface works properly; there is just not enough of it.

Clinical Manifestations

- CF is a chronic, insidiously progressive disease exhibiting multiple complications related to viscous mucus, malabsorption and infection.
- It is called a sino-pulmonary disease and the patient might have chronic sinusitis and/or nasal polyps. (common)
- Digital clubbing (without any significant lung disease)
- Allergic bronchopulmonary aspergillosis = Hypersensitivity to Aspergillosis (we give steroids and antifungal)
- Chronic bronchial infection leads to cough (most common initial pulmonary manifestation), sputum production, hyperinflation, bronchiectasis and eventually pulmonary insufficiency.
- Most patients are colonized with Haemophilus influenza, Staphylococcus aureus or Pseudomonas aeruginosa (which predominates in older patients with advanced disease).

- Exocrine pancreatic insufficiency :
 - Fat Malabsorption
 - 1- Steatorrhea (large, fatty, floating, foul-smelling stool)
 - 2- Deficiency in fat soluble vitamins (vitamins K, A, D, E)
 - Protein Malabsorption
 - 1- Hypoproteinemia
 - 2- Peripheral edema
- Nutrient malabsorption can result in failure to thrive despite good appetite.
- Intestinal obstruction:
Caused by (meconium ileus) or (distal intestinal obstruction syndrome) in older patients.
- In males: Congenital absence or atrophy of vas deference & azoospermia.
- In females: 2ry amenorrhea & a decrease in fertility but can conceive.
- Poor ciliary motion in fallopian tubes due to secretions but no disease in cilia.

- Presentation according to age:

Neonates

- 1) Meconium ileus (most common)
- 2) Prolonged jaundice.
- 3) Syndrome of hypoalbuminemia anemia.

Children

- Rarely before the age of 2 years usually > 5 years.
- 1) Nasal polyps (recurrent even after surgery)

- 2) Sinusitis, haemoptysis, chest pain...
 - 3) Intussusception, volvulus, distal intestinal obstruction, recurrent Abdominal pain.
 - 4) Gall bladder stones, hepatomegaly, ascites...
 - 5) Rectal prolapse with Steatorrhea, malnutrition & cough.
- Dehydration in CF :
 - Low levels of fluids & electrolytes (HYPO- Na⁺, CL⁻)
 - Recurrent in infancy
(Any recurrent unexplained hypotonic dehydration in an infant-- think of CF)
 - 2ry metabolic alkalosis.
 - Treatment: IV 0.9% NS for CL⁻ responsive metabolic alkalosis.
 - Progressive pancreatic damage can lead to Insulin deficiency, this initially presents as glucose intolerance then later as Diabetes in 2nd decade of life. (CF- related diabetes)
 - Any child with [1) nasal polyps 2) rectal prolapse] should be screened for CF regardless the age.
 - Cardiac system and CNS are not primarily involved. (Chronic pulmonary HTN can 2ry affect the heart)
 - Renal system can be secondarily involved due to drugs used in treatment.

Note:

Differential diagnosis of pan-sinusitis in children (top 3):

- 1- Cystic Fibrosis.
- 2- Primary ciliary dyskinesia (PCD).
- 3- Immunodeficiency.

Diagnostic studies

- Sweat test (Diagnostic test of choice),(specific & sensitive)
- Criteria to diagnose CF:
 - Presence of one or more typical features of CF (Chronic pulmonary disease, GI & nutritional abnormalities, salt loss syndrome or obstructive azoospermia) **AND**
1) 2 elevated sweat CL⁻ test (+ve if >60 mEq/l).

- 2) 2 mutations known to cause CF identified by DNA analysis
OR
- 3) A Characteristic abnormality in ion transport across nasal epithelium demonstrated in vivo (**Nasal potential difference testing**)

- If +ve newborn screening or sibling has CF, only criteria is :
 - 1) +ve sweat CL^- test **OR**
 - 2) Presence of known disease causing DNA mutation.
- Other supportive tests:
 - Measurement of fecal elastase levels (Low fecal elastase indicate exocrine pancreatic insufficiency) - screening test.
 - Measurement of bioelectrical potential differences across nasal epithelium (not widely available)
 - Immune-reactive trypsinogen (screening test, not diagnostic).

Causes of CF false positive and false negative Sweat test

False Positive
Adrenal insufficiency
Dehydration
Malnutrition
Poor technique/ inadequate sweat collection
Type 1 glycogen storage disease
Pan hypopituitarism
Pseudohypoaldosteronism
Hypoparathyroidism
Prostaglandin E1 administration
Eczema
Ectodermal dysplasia
Nephrogenic diabetes insipidus
Hypothyroidism
Fucosidosis
Mucopolysaccharidosis
False Negative
Edema
Poor technique/ inadequate sweat collection
Atypical cystic fibrosis (unusual gene mutation- uncommon)

Treatment

- The treatment of CF is multifactorial.
- It is primarily directed toward gastrointestinal and pulmonary complications.
- There is no effective single cure for CF.
- Management of pulmonary complications is directed toward facilitating clearance of secretions from airways and minimizing the effects of chronic bronchial infections.
 - 1- Chest physiotherapy (for airway secretion clearance, the main treatment and the most important, daily treatment).
 - 2- (Aerosolized DNase + 7% hypertonic saline) delivered by nebulizer, decrease the viscosity of mucus.
 - o Mucolytic agents don't work on thick mucus, we give DNase.
 - 3- Antibiotic therapy
 - o Important in controlling chronic infections.
 - o Selected based on organism identified by sputum culture.
 - o Give 2 types for synergism.
 - o It is given at least 14 days
 - o Common Organisms: Staph. Aureus & Pseudomonas aeruginosa.
 - o Tobramycin: inhalational antibiotic.
 - 4- Lung transplant is the ultimate treatment for chronic respiratory Failure/ 100% therapeutic but the problem is that we give Immunosuppressant.
 - 5- For Exocrine pancreatic insufficiency patients are encouraged to follow a high caloric diet in addition to pancreatic enzyme replacement (i.e. Lipase)
 - 6- Fat soluble vitamins are recommended ADEK/ enzyme supplements.
 - 7- CF- related diabetes is treated with Insulin.
 - 8- Newborns with meconium ileus may require surgical intervention.
 - 9- Intestinal obstruction in patients beyond the neonatal period may need to be treated with courses of oral laxatives.

Antihistamines not used for CF, neither for cough nor intrinsic asthma. It can be given in extrinsic asthma only to prevent the reaction that leads to asthma.

Prognosis

- Only 1-3% of patients have progressive cirrhosis resulting in portal hypertension.
- The majority of patients die with pulmonary complications.
- Median age of survival is currently in the mid-30s.

Sources: 1) Nelson Essentials of Pediatrics, 7th edition.

2) Notes from lecture.

Done by: Farah Amer

Some notes were added by Rafeef Qawasmeh (from Dr. Muna Khater seminar)

Immunology
&
Allergies

Immunology & allergy

When to suspect immunodeficiency?

10 warning signs of primary immunodeficiency:

1. 4 or more new ear infections within 1 year.
2. 2 or more serious sinus infections within 1 year.
3. 2 or more months on antibiotics with little effect.
4. 2 or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. 2 or more deep-seated infections including septicemia.
10. A family history of 1ry immunodeficiency.

Initial screening for recurrent infections: CBC, manual differential, platelet count, smear. What normal values tell you?

- Normal absolute lymphocyte count: unlikely T-cell defect.
- Normal absolute neutrophil count: eliminates congenital or acquired neutropenia and both forms of leukocyte adhesion deficiency.
- Normal platelet count: excludes Wiskott-Aldrich syndrome.
- Howell-Jolly bodies: suggest asplenia.
- Normal ESR: excludes chronic bacterial or fungal infection.

The following topics are mainly from Kaplan with some notes from Nelson Essentials. Also, there are questions in-between topics from Dr. Adel Wahadneh with some clarifications for answers.

1. Which test is MOST helpful to evaluate cell mediated immunity in a 3 yr old child with recurrent infections, chronic diarrhea, and failure to thrive?
 - A. Quantitative immunoglobulin Measurement (IgA, IgG, IgM).
 - B. Give immunizations and then measure specific antibody titers 6 weeks later.
 - C. Nitroblue tetrazolium dye reduction test.
 - D.** PPD and control delayed skin tests.
 - E. Measure complements levels.

Clarification: according to the table in the next page, this clinical presentation (recurrent infections, chronic diarrhea, and FTT) increases the suspicion toward T-cell immunodeficiency, answer D is the most relevant answer.

Evaluation of immune mediated diseases			
Suspected deficiency	Clinical presentation	Initial labs	Definitive
B cell	Recurrent infections with encapsulated bacterial, enteroviral and hepatitis viruses	Quantitative immunoglobulins: normal IgA excludes most of them	Flow cytometry using monoclonal antibodies to B cell specific CD antigen. Then, molecular diagnosis if no previous family history.
T cell	Recurrent opportunistic infections with chronic diarrhea and FTT	Absolute lymphocyte count (normal count precludes the Dx) if low count do candida intradermal skin test	Mitogen stimulation for function, then flow cytometry, then molecular diagnosis if no previous family history.
Phagocytic	Recurrent staph and gram negative infections	Respiratory burst assay using rhodamine dye/ flow cytometry for CD antigens specific for leukocyte adhesion deficiencies.	Molecular diagnosis
Complement	Pyogenic infections/ life threatening septicemia/ Neisseria infections.	CH50	Specific complement assays/ molecular diagnosis

2. A 5 year old male is admitted with his third episode of bacterial meningitis. Each time, the culture has grown *Neisseria meningitidis*. Which of the following tests is most likely to find the underlying immune deficiency responsible for these recurrent infections?
- A. Nitroblue tetrazolium dye reduction test
 - B. Quantitative immunoglobulins
 - C. Flow cytometry for adhesion molecules
 - D. CH50**

Clarification: according to the table above, *Neisseria* infection indicates complement deficiency; CH50 is the initial lab test.

Defects of antibody production (B-cell defects)

- * Bruton agammaglobulinemia.
- * Common variable immune deficiency.
- * Selective IgA deficiency.
- * IgG subclass deficiency.

Bruton agammaglobulinemia

- X-linked B cell immune deficiency; fine until age of 6 – 9 months.
- The defect is caused by mutations in a gene encoding the tyrosine kinase Btk on chromosome Xq22 that is involved in a signaling of the pre-B-cell receptor and the B-cell antigen receptor.
- Extracellular pyogenic infections (S.pneumonia, H.influenza, M.pneumonia)/ hepatitis viruses/ enteroviruses.
- Lymphoid hypoplasia (tonsils and adenoids; no splenomegaly or lymphadenopathy).
- Significant decrease in all immunoglobulins.
- Flow cytometry: absence of circulating B cells.
- Treatment: monthly IVIG and antibiotics for infections.

Common variable immune deficiency	Selective IgA deficiency	IgG subclass deficiency
<ul style="list-style-type: none"> * Hypogammaglobulinemia with phenotypically normal B cells. * Acquired/ later age of onset/ equal sex distribution. * Infections like Bruton but rare enteroviral meningitis. * Normal or increased lymphoid tissue. * Significant autoantibody production to IgA. * Significant increase in lymphomas (esp. women in 5th to 6th decade). 	<ul style="list-style-type: none"> * Most common B cell defect. * Near absence of serum and secretory IgA. * Equal sex distribution. * Respiratory, GI, urogenital, and skin infections. * High incidence of autoimmune disease and increased malignancies. * Serum antibodies to IgA. * Fatal anaphylactic reactions if given blood with IgA. 	<ul style="list-style-type: none"> * IgG is a combination of 4 slightly different types of IgG called IgG subclasses: IgG1, IgG2, IgG3 and IgG4. * One or more of the 4 subclasses are decreased despite normal or even increased total IgG. * IgG2 is the most to be decreased. Accompanied with IgA deficiency. * May be an early marker for more general immune dysfunction. * No IVIG unless there are deficiencies of antibodies to broad array of antigens.

3. A 12 month old infant was diagnosed with X-linked agammaglobulinemia (XLA), a recessive B cell immune deficiency, after suffering multiple sinopulmonary tract infections such as otitis media, sinusitis and pneumonia. What is an appropriate treatment for him?
- A. Plasmapheresis and broad spectrum antibiotics
 - B. Intravenous immunoglobulin (IVIG).**
 - C. Prophylactic antibiotics
 - D. Enzyme replacement therapy

Defects of cellular immunity (T cell defects)

*More severe than B-cell defects; no survival beyond infancy or early childhood without definitive treatment.

* DiGeorge syndrome.

DiGeorge syndrome

- Also known as velocardiofacial syndrome or CATCH 22 syndrome (cardiac anomalies, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia).
 - It is the result of dysmorphogenesis of the third and fourth pharyngeal pouches, resulting in hypoplasia of the thymus required for T-cell maturation/ T-cell immune deficiency.
 - Most, but not all patients, have a defect on chromosome 22q11.2
 - Dysmorphic features: short philtrum/ hypertelorism/ mandibular hypoplasia/ fish mouth/ low-set large notched ears.
 - Decreased or absent thymic tissue with normal lymphoid tissue.
 - Treatment: transplantation of thymic tissue of MHC-compatible sibling or half matched parenteral bone marrow.
 - Diagnosis:
 - ✓ Low absolute lymphocyte count; decreased IgA and increased IgE
 - ✓ Absent respiratory burst to mitogens.
4. A 2 week old boy is admitted to the hospital for seizures and found to have hypocalcemia. Physical exam is significant for hypertelorism, mandible hypoplasia and a loud systolic murmur. What immunodeficiency should you suspect?
- A. Ataxia-telangiectasia
 - B. X-linked hyper-IgM syndrome
 - C. DiGeorge Syndrome**
 - D. Severe combined immunodeficiency (SCID)

Severe combined immunodeficiency (SCID)

- Combined antibody and cellular defect.
- Absence of all adaptive immune function and perhaps natural killer function.
- Types: X-linked (m.c) and AR.
- Classic presentation:
 - ✓ First few months of life.
 - ✓ Opportunistic and viral infections (C.albicans, P.carinii, varicella, measles, parainfluenza 3, CMV, EBV).
 - ✓ Diarrhea, extreme wasting.
 - ✓ Pneumonia, otitis media, sepsis, cutaneous infections.
 - ✓ Graft versus host disease from maternal immunocompetent T cells crossing placenta.
 - ✓ Severe lymphopenia from birth/ small or no thymus/ absent lymphoid tissue.
 - ✓ No mitogen response/ no immunoglobulins/ no antibody response.
- Treatment: this is a true pediatric emergency; bone marrow transplant or death by 1 year of age. If diagnosed in first 3 months of life, >95% treated successfully (more recent – gene therapy).

Chronic granulomatous disease (CGD)

- It is a phagocytic defect/ X-linked and AR
 - Findings: recurrent lymphadenitis/ pneumonia/ skin infections/ hepatic abscesses/ osteomyelitis at multiple sites.
 - Infections with catalase positive organisms; staphylococcus aureus is the most common.
 - Diagnosis: nitroblue tetrazolium test (NBT) now replaced by flow cytometry test using dihydrohodamine 123 fluoresce (DHR test).
 - Treatment: bone marrow transplant
5. A 15 month old female has been hospitalized for several serious infections secondary to Staphylococcus aureus including osteomyelitis, hepatic abscess and pneumonia with pneumatocele formation. What is the most likely diagnosis?
- A. Wiskott-Aldrich Syndrome
 - B. Selective IgA deficiency
 - C. Leukocyte adhesion deficiency
 - D. Chronic granulomatous disease (CGD)**
6. What is the BEST test for diagnosis of chronic granulomatous disease (CGD)?
- A. Immunoglobulin levels
 - B. Nitroblue tetrazolium test**
 - C. Absolute neutrophil count
 - D. Absolute T and B cell count

Combined immunodeficiencies

*Wiskott-Aldrich syndrome.

*Ataxia telangectasia

Feature	Wiskott-Aldrich syndrome	Ataxia telangectasia
Problem	T cells moderately decreased. Impaired humoral response (Moderate decrease in response to B- and T-cell mitogens.
Genetics	X-linked recessive (WAS protein).	A-T mutation on chromosome 11 (11q22-23); protein kinase.
Infections	Pyogenic infections with encapsulated bacteria in 1 st year. Later, opportunistic infections.	Chronic sinopulmonary infections (good prognosis).
Findings	Atopic dermatitis (in first year)/ thrombocytopenia with normal megakaryocytes but small defective platelets (petechiae). Palpable adenopathy/ splenomegaly and lymphadenopathies/ prolonged bleeding from circumcision.	Hypoplastic thymus (helper T-cell defects, mask-like faces, tics, drooling, irregular eye movements). Oculocutaneous telangectasias (age 3-6 years). Progressive cerebellar ataxiawith start of walking/ wheelchair by age of 10-12 years.
Lab findings	Neutropenia/ decreased mitogen response/ Ig highly variable but most with ↓ IgM, ↑ IgA, ↑ IgE and normal or slightly low IgG.	Decreased CD3 and CD4 cells. Variable humoral and cellular deficiency (most with selective IgA deficiency).
Complications	Malignancy/ infections/ bleeding.	High incidence of malignancies (lymphoreticular but also adenocarcinoma).
Treatment	Manage skin disease/ aggressive treatment of infections/ platelet transfusion and splenectomy/ bone marrow transplant (rare survival beyond teens without transplant).	Physical therapy/ manage infections aggressively/ IVIG (if not selective IgA).

Urticaria and angioedema

- Occur in response to the release of inflammatory mediators, including histamine, leukotrienes, platelet-activating factor, prostaglandins, and cytokines from mast cells present in the skin.
 - Acute (≤ 6 weeks); causes: foods/ medications/ insect stings/ infections/ contact allergy/ transfusion reactions/ idiopathic.
 - Chronic (>6 weeks); causes:
 - ✓ Idiopathic (the most common).
 - ✓ Physical urticaria (environmental factors; temperature, pressure, stroking, vibration, light).
 - ✓ Rheumatologic (SLE, juvenile idiopathic arthritis).
 - ✓ Endocrine (hypo- and hyperthyroidism).
 - ✓ Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor).
 - ✓ Neoplastic: lymphoma/ mastocytosis/ leukemia.
 - Diagnosis mainly clinical; skin tests with IgE-specific allergens.
 - Treatment: avoidance of triggers/ oral antihistamines/ epinephrine and short burst corticosteroids in severe cases/ if H1 antagonist alone doesn't work combine with H2 antagonist and consider using steroids/ for chronic refractory cases use IVIg or plasmapheresis.
7. A 12 year old girl presents with a 3 month history of daily urticaria with pruritus and occasional episodes of lip and eyelid swelling. What is the most likely cause for her urticaria and angioedema?

- A.** Idiopathic
- B. Hidden food allergy
- C. Contact allergy to dust mites or family pet
- D. Underlying autoimmune disease
- E. C1 inhibitor deficiency

Clarification: Chronic urticaria and angioedema are characterized by persistence of symptoms beyond 6 weeks. This 3-month history indicates chronic urticaria and angioedema. The most common cause is idiopathic.

Anaphylaxis

- Sudden release of active mediators with cutaneous, respiratory, cardiovascular, or GI symptoms.
- Reasons:
 - ✓ In hospital: latex, antibiotics, IVIG, radiocontrast agents.
 - ✓ Out of hospital: food (most common is peanuts), insect sting, oral medications, idiopathic.

- Presentation: reactions from ingested allergens are delayed (minutes to 2 hours); with injected allergen reaction is immediate and more GI symptoms.
 - Treatment:
 - ✓ Immediate: injectable epinephrine/ oral liquid diphenhydramine/ transport to ER.
 - ✓ Oxygen and airway management.
 - ✓ Epinephrine IM (IV for severe hypotension); intravenous fluid expansion.
 - ✓ H1 antagonist/ corticosteroids/ nebulized short-acting beta 2 agonist (with respiratory symptoms)/ H2 antagonist (if oral allergen).
8. A 7 year old boy has a history of an adverse reaction to radiocontrast media (RCM) 2 years ago which included diffuse pruritus and urticaria accompanied by hypotension. Which statement is TRUE regarding his adverse reaction to RCM?
- A. History of this type of reaction is an absolute contraindication to further administration of RCM.
- B. He should avoid RCM and iodine, such as in iodine cleaning solutions and shellfish.
- C. He should receive high-osmolar, ionic RCM for the next procedure.
- D.** He should receive antihistamines and prednisone prior to next procedure with RCM.

Atopic dermatitis (Eczema)

- Interaction among genetic, environmental and immunologic factors; familial with strong maternal influence.
- Majority develop allergic rhinitis and/or asthma.
- Most have increased eosinophils and IgE.
- **Presentation:** half start by age 1 year; most by age 1 and 5 years; chronic or relapsing.
 - ✓ Intense cutaneous reactivity and pruritus; worse at night.
 - ✓ Exacerbations with foods, inhalants, bacterial infection, irritants, excessive sweating, decreased humidity.
 - ✓ Acute pattern of skin reactions: erythematous papules/ intensely pruritic/ serous exudate, excoriation.
 - ✓ Subacute pattern: erythematous, excoriated, scaling papules.
 - ✓ Chronic pattern: lichenification.
 - ✓ Distribution: infancy (face, scalp, extensor surfaces of extremities); older, long standing disease (flexural aspects); remission with age, but skin left prone to itching and inflammation when exposed to irritants.
- **Treatment:**
 - ✓ Eliminate causative factors.
 - ✓ Cutaneous hydration.
 - ✓ Topical corticosteroids (emollients and low potency steroids for maintenance).

- ✓ Topical immunomodulators (tacrolimus; safe on face; can be used in young-2 years).
 - ✓ Tar preparations.
 - ✓ Phototherapy – UV light.
 - ✓ Antibiotics for bacterial superinfection.
 - ✓ Systemic: antihistamines/ glucocorticoids or interferon if other treatment failed.
- **Complications:** 2ry bacterial infection (*S.aureus*); increased incidence of *T.rubrum* and *M.furur*/ recurrence viral skin infections – Kaposi varicelliform eruption (eczema herpeticum) most common/ warts/ molluscum contagiosum.

Contact dermatitis

- Irritant: nonspecific injury to the skin results from prolonged or repetitive contact with various substances (e.g. diaper rash).
- Allergic: delayed hypersensitivity reaction (type IV) provoked by antigen applied to skin/ intense itching can mimic atopic dermatitis/ causes: jewelry (nickel), shoes, clothing, and plants (poison ivy).
- Diagnosis: clinical.
- Treatment: supportive; eliminate contact with allergen; cool compresses.

Food reactions

- Most infants and young children outgrow milk and egg allergy (half in first 3 years); but most children with nut or seafood allergies retain the allergy for life.
- Most food allergies are egg, milk, peanuts, nuts fish, soy and wheat; but any food may cause a food allergy.
- Food allergic reactions are most common cause of anaphylaxis seen in emergency rooms.
- With food allergies, there is an IgE and/or a cell mediated response.
- **Manifestations:**
 - ✓ Skin: urticarial/ angioedema/ flushing/ atopic dermatitis (1/3 of children with atopic dermatitis have food allergies).
 - ✓ GI: oral pruritus/ nausea and vomiting/ diarrhea/ abdominal pain/ eosinophilic gastroenteritis (a cell mediated response, so standard allergy tests are of little value/ food protein induced enterocolitis that presents with bloody diarrhea).
 - ✓ Respiratory: nasal congestion/ rhinorrhea/ sneezing/ laryngeal edema/ wheezing/ asthma.
 - ✓ CVS: hypotension/ dysrhythmias.
- **Diagnosis:** skin tests, IgE-specific allergens are useful for IgE sensitization. A negative skin test excludes an IgE-mediated form, but for cell-mediated responses, a food elimination and challenge test is needed.

- **Treatment:** only validated treatment is elimination/ epinephrine pens for possible anaphylaxis.
9. You are seeing a 3 year old girl and her 5 year old brother for a well-child check-up. Both have food allergies. Her mother asked you about the likelihood that they will outgrow their food allergies. What is the BEST response to her question?
- A. Most children do not outgrow food allergies
 - B. Children with egg allergy are not likely to outgrow the allergy
 - C.** Children with peanut allergy are not likely to outgrow the allergy
 - D. Children with soy allergy are not likely to outgrow the allergy

Insect venom allergy

- Systemic allergic responses are IgE mediated and almost due to stings from the order Hymenoptera (yellow jackets most notorious).
- Presentation: local (limited swelling and pain less than 1 day duration)/ large local area (extensive swelling over hours to days)/ systemic (urticaria, angioedema, anaphylaxis, pruritus)/ toxic (fever, malaise, emesis, nausea)/ delayed response (serum sickness, nephrotic syndrome, vasculitis, neuritis, encephalitis).
- Diagnosis: skin testing.
- Treatment:
 - ✓ Local: cold compressors/ topical antipruritic/ oral analgesic/ systemic antihistamine/ remove stingers by scraping.
 - ✓ Anaphylaxis: epinephrine.
 - ✓ Severe reaction with positive skin tests: venom immune therapy.

Allergic rhinitis

- Allergic rhinitis, commonly known as hay fever, is caused by an IgE-mediated allergic response.
- Generally established by 6 years of age.
- Diagnosis suggested by typical symptoms in absence of URTI or structural abnormality (nasal congestion/ pruritus, worse at night with snoring, mouth-breathing; watery itchy eyes; postnasal drip with cough; possible wheezing; headache).
- Vigorous grinding of eyes with thumb and side of fist.
- Family history of allergic disease (atopy, asthma).
- **Physical examination:**
 - ✓ Allergic shiners (blue-grey-purple beneath lower eyelids).
 - ✓ Dennie lines (prominent symmetric skin folds beneath lower eyelids).

- ✓ Conjunctival injection, chemosis, stringy discharge, cobblestoning of tarsal conjunctiva.
 - ✓ Transverse nasal crease from allergic salute.
 - ✓ Pale nasal mucosa, turbinate hypertrophy, polyps.
 - ✓ Postnasal drip.
 - ✓ Otitis media with effusion.
- DDx: non-allergic inflammatory rhinitis/ vasomotor rhinitis/ nasal polyps/ septal deviation/ overuse of topical vasoconstrictors.
- **Diagnosis:**
 - ✓ No initial routine labs; it is a clinical diagnosis.
 - ✓ Peripheral eosinophilia.
 - ✓ Increased serum IgE.
 - ✓ IgE-specific allergen in blood-draw.
 - ✓ Skin test.
- **Treatment:**
 - ✓ Environmental control plus removal of allergen is most effective method.
 - ✓ Antihistamines (first line therapy): first generation (sedating)/ 2nd generation; cetirizine, loratidine (non-sedating, easier dosing, preferred). Oral antihistamines are more effective than cromolyn but significantly less than intranasal steroids.
 - ✓ Intranasal corticosteroids (most effective medication but not first line).
 - ✓ Leukotriene receptor antagonists.
 - ✓ Chromones (cromolyn and nedocromil sodium): least effective, very safe with prolonged use.
 - ✓ Decongestants (alpha adrenergic).
 - ✓ Epinephrine (drug of choice for anaphylaxis).
 - ✓ Immunotherapy: administer gradual increase in dose of allergen mixture to decrease or eliminate person's adverse response on subsequent natural exposure.
- **Complications:** chronic sinusitis/ asthma/ Eustachian tube obstruction/ tonsil hypertrophy/ emotional and psychological problems.

10. A 12 year old male is receiving allergy shots in your general pediatric clinic for allergic rhinitis. Approximately 30 minutes after his shot, he has erythema at the injection site. His vital signs include BP for 120/70, HR 80, RR 15 and oxygen sat of 97% on RA. Aside from a raised, quarter sized area of erythema on his upper right arm at the injection site, his physical exam is normal. What should you do for this patient?

- A. Give intramuscular epinephrine
- B. Recommend that he stop his allergy shots

- C. Observe the patient for 1 hour.
- D. Send the patient home

Clarification: this presentation indicates anaphylactic reaction. The drug of choice for anaphylaxis is epinephrine.

Asthma

- It is a chronic inflammation of airways with episodic partially reversible airflow obstruction.
- Most with onset before 6 years and resolve by late childhood.
- Early childhood asthma triggered primarily by common viral infections.
- Chronic asthma associated with allergies.
- Presentation: diffuse wheezing (expiratory then inspiratory)/ prolonged expiratory phase/ rales/ exercise intolerance decreased breath sounds.
- Allergic asthma is an extrinsic asthma with elevated levels of IgE. Triggers must contain protein (Food (milk, wheat, eggs, fish and nuts)/ Pollens/ Spores of fungi/ Dust mites/ Cat dander/ dogs/ birds/ rabbits/ hamsters).

- **Diagnosis:** spirometry during forced expiration is the gold standard/ peak expiratory home monitoring.
 - ✓ Bronchodilator response to inhaled beta agonist: improvement in FEV1 to >12%.
 - ✓ Exercise challenge: worsening in FEV1 of at least 15%.
 - ✓ X-ray to exclude other problems (no routine use).

- **Quick relief medications:**
 - ✓ Short acting beta 2 agonists: albuterol (salbutamol "Ventolin"), nebulized levalbuterol/ drug of choice for exercise induced asthma.
 - ✓ Anticholinergics (ipratropium bromide/ for added treatment of acute severe asthma).
 - ✓ Short course systemic glucocorticoids (prednisone for outpatient with flare-up/ IV methylprednisolone in hospital).
 - ✓ Oxygen (if hypoxic; in asthma exacerbations).

- **Long term medications for control:**
 - ✓ Cromolyn sodium.
 - ✓ Inhaled corticosteroids (treatment of choice for persistent asthma).
 - ✓ Long acting beta agonists (salmeterol and formoterol, add-on medication, not safe and must be used with inhaled corticosteroids).
 - ✓ Leukotriene modifying agents (2 classes): inhibitors of synthesis (zileuton; >12 years old)/ receptor antagonists (montelukast).
 - ✓ Systemic steroids (for severe asthma).
 - ✓ Theophylline: rarely used anymore due to narrow therapeutic index.

Class	Daytime symptoms	Nighttime symptoms	Treatment
Intermittent	<= 2/week	<= 2/month	Short acting beta agonist
Mild persistent	>2/week	>2/month	Inhaled steroids/ short acting beta agonist for breakthrough
Moderate persistent	Daily	>1/week	Inhaled steroids/ long acting beta agonist/ short acting beta agonist for breakthrough/ leukotriene-receptor antagonists.
Severe persistent	Continual; limited activities; frequent exacerbations	frequent	High dose inhaled steroid/ long acting beta agonist/ short acting beta agonist for breakthrough/ leukotriene-receptor antagonists/ systemic steroids.

11. A 12 year old patient with severe asthma was admitted to the hospital for an acute asthma exacerbation and has been treated with a variety of medications including salbutamol over the past 24 hours. You are concerned that he might have symptoms related to salbutamol toxicity. Which of the following is NOT a side effect of inhaled salbutamol?

- A. Muscle tremor
- B. Hypotension**
- C. Hypokalemia
- D. Tachycardia
- E. Nervousness

12. A 3 years old asthmatic boy who is maintained on Montelukast and high dose inhaled fluticasone, reported to come 3 times to ER in the past 2 months, and used rescue Salbutamol repeatedly, the appropriate next step in the treatment of this patient is :

- a) Keeping him on maintenance prednisone PO
 - b) Asking for skin prick test (SPT).
 - c)** Adding Formoterol
 - d) Ordering RAST test for inhalational allergens
 - e) Giving oral aminophylline
13. A 5 year old patient with severe asthma who was found to require mechanical ventilation. He may benefit from which of the following initial ventilator parameters?
- a) Rapid rates, short inspiratory times, and tidal volumes <6 mL/kg
 - b) Low rates, prolonged inspiratory/expiratory times, and low tidal volumes (<6 mL/kg)
 - c)** Low rates, prolonged inspiratory/expiratory times, and moderate tidal volumes (8-10 mL/kg)
 - d) Low rates, prolonged inspiratory/expiratory times, and high tidal volumes (>15 mL/kg)
14. Which of the following physical findings would be least likely on examination of a child with moderate to severe asthma?
- a) Tachypnea.
 - b) Wheezing.
 - c) Clubbing.**
 - d) Decreased air exchange over the right middle lobe.
 - e) Increased AP diameter of the chest.

Explanation: Digital clubbing is rarely observed in children with uncomplicated asthma and should prompt evaluation to exclude other potential diagnoses.

15. A 12-yr-old girl with moderate to severe asthma is sensitive to cat dander. Her family elects to remove the pet cat from the house, but to retain the present carpeting and upholstered furniture. What is the length of time required before the levels of cat allergen drop to levels found in homes without a cat?
- a. Immediately
 - b. 2 days
 - c. 2 wk
 - d. 2 mo
 - e.** 6 mo

Explanation: Cat owners who remove the cat from the home without also removing carpeting and upholstered furniture, and thoroughly wiping down all walls and hard surfaces, should be informed not to expect immediate

results. It may take 6 months to 1 year for the levels of cat allergen to drop to a level found in homes without a cat.

16. The parents of a 3-yr-old girl with a history of several previous coughing and wheezing exacerbations are wondering if their toddler is likely to develop persistent asthma. Which of the following is a strong risk factor for persistent asthma in toddlers with recurrent wheezing?
- a. Eczema **
 - b. Colic.
 - c. Living in a farm.
 - d. Female gender.
 - e. Otitis media with effusion.

Explanation: Only a minority of young children who experience recurrent wheezing will go on to have persistent asthma in later childhood. Several risk factors have been identified; eczema is a strong one.

17. A 10-yr-old child has intermittent symptoms of mild asthma. The most appropriate treatment option is:
- a. Environmental control and patient education only? no medication is indicated
 - b. Oral theophylline
 - c. Cromolyn
 - d.** Inhaled beta 2-agonist as needed for symptoms
 - e. Daily inhaled corticosteroid

Explanation: For mild intermittent symptoms of asthma, recommended treatment is with a short-acting inhaled 2- agonist as needed for symptoms. The intensity of treatment depends on the severity of exacerbations. The need for short-acting inhaled 2-agonist use more than two times a week may indicate the need to initiate long-term-control therapy.

18. The child described in the previous question experiences worsening of symptoms, which are now persistent and of moderate severity. The most appropriate treatment option is:
- a. Oral theophylline
 - b. Inhaled beta 2-agonist as needed for symptoms
 - c. Daily inhaled corticosteroid and oral theophylline
 - d.** Daily inhaled corticosteroid and a long-acting inhaled 2 agonist
 - e. Daily inhaled corticosteroid, a long-acting inhaled 2-agonist, and oral theophylline

Explanation: For moderate persistent symptoms of asthma, recommended treatment is with a daily-inhaled corticosteroid and a long-acting inhaled 2-

agonist. Alternatives to the inhaled 2-agonist are sustained-release theophylline and a leukotriene receptor antagonist. In addition, for moderate persistent symptoms of asthma, a short-acting 2-agonist is also used as needed for quick relief of symptoms.

19. A 12-yr-old asthmatic boy has developed an asthma exacerbation in the past few days. Asthma symptoms have continued to progress despite frequent albuterol use at home. He comes to the emergency department with chest tightness, dyspnea, and wheezing, and in moderate respiratory distress. In this setting, management should include all of the following except:

- a. Close monitoring
- b. Supplemental oxygen
- c. Inhaled albuterol
- d. Theophylline**
- e. Systemic glucocorticoids

Explanation: Initial emergency department management of an asthma exacerbation includes close monitoring of clinical status, treatment with supplemental oxygen, inhaled -agonist every 20 min for 1 hr, and if necessary, systemic glucocorticoids (2 mg/kg/day) given either orally or intravenously. Inhaled ipratropium may be added to the -agonist treatment if no significant response is seen with the first inhaled -agonist treatment. If a child responds poorly to intensive therapy with nebulized albuterol, ipratropium, and parenteral glucocorticoids, then adding intravenous theophylline could be considered.

20. A 7-yr-old girl has had intermittent asthma symptoms over the past 5 yr. Her asthma symptoms have been treated with inhaled albuterol as needed. She mostly has exercise-induced asthma symptoms, which happens on most school days except when she uses her albuterol inhaler before going to recess and physical education classes. In the past year, she has had two asthma exacerbations with viral upper respiratory tract infections, and she has used a total of 5 albuterol metered-dose inhalers. The most appropriate management for this asthmatic girl is:

- a. Continue albuterol as needed and before physical exercise activities.
- b. Begin daily controller medication with an inhaled glucocorticoid, initially used more frequently to gain control, then a reduced amount in a few months to maintain control **
- c. Begin daily inhaled glucocorticoid in a low dose, increasing the dose monthly until good control is obtained.
- d. Administer daily oral glucocorticoid treatment for one week, with concurrent daily inhaled glucocorticoid.
- e. Begin use of a long-acting beta inhaled -agonist each morning.

Explanation: Low-dose inhaled glucocorticoids, leukotriene pathway modifiers, and cromolyn/nedocromil are the recommended controllers for mild persistent asthmatics; sustained-release theophylline is an alternative.

21. A 6-year-old male is brought in for evaluation by his mother, who is concerned that he may have asthma. She reports that he coughs about 3 days out of the week and has a nighttime cough approximately 1 night per week. There is a family history of eczema and allergic rhinitis. Which one of the following would be the preferred initial treatment for this patient?
- A. A leukotriene receptor antagonist such as Singulair
 - B.** A low-dose inhaled corticosteroid such as budesonide
 - C. A long-acting beta-agonist such as salmeterol
 - D. A mast-cell stabilizer such as cromolyn sodium

Explanation: daytime symptoms > 2 times/ week and night symptoms > 2 times/ month. This indicates mild persistent asthma which its treatment is inhaled steroids and beta agonists for breakthrough.

22. Which one of the following statements about the use of salmeterol (Serevent) to treat moderate asthma is correct?
- A. It is safe to use salmeterol alone .
 - B. It is a convenient alternative to albuterol .
 - C.** It may be used in combination with inhaled corticosteroids and albuterol in adults .
 - D. Patients taking salmeterol should be switched to formoterol (Foradil).

Explanation: salmeterol is one of long acting beta agonists which are not safe and must be used with inhaled corticosteroids.

23. In which one of the following situations should a physician consider “stepping down” therapy for a patient with asthma?
- A. When the patient has had three nighttime awakenings in one week .
 - B. When the patient has an FEV1 or peak flow of 60 to 80 percent personal best .
 - C.** When the patient has been stable with well-controlled asthma for at least three months .
 - D. When the patient has had two exacerbations per year requiring oral corticosteroids .

Explanation: The guidelines recommend that treatment be reevaluated within 2 to 6 weeks of initiating therapy. Once asthma is under control, control should be assessed on an ongoing basis every 1 to 6 months. The asthma should be well controlled for at least 3 months before stepping down therapy.

24. Which one of the following is true concerning control of mild persistent asthma in the pediatric population?
- A. Cromolyn sodium should not be used for chronic control of asthma in children under 5 years of age.
 - B. Inhaled anticholinergic agents, such as ipratropium, should be added if inhaled beta-adrenergic agents do not maintain control of asthma.
 - C. A long-acting beta-agonist should be added if a short-acting beta-agonist is ineffective.
 - D.** Inhaled anti-inflammatory agents, such as glucocorticoids or cromolyn sodium, should be used initially to maintain chronic control of asthma.
25. Which one of the following is the preferred first-line therapy for ongoing management of chronic asthma?
- A. Theophylline .
 - B.** Inhaled corticosteroids .
 - C. Inhaled cromolyn (Intal).
 - D. Leukotriene receptor antagonists
26. A 12-year-old white male asthmatic has an acute episode of wheezing. You diagnose an acute asthma attack and prescribe an inhaled beta2-adrenergic agonist, but despite 1–2 hours of treatment he continues to experience wheezing and shortness of breath. Which one of the following is the most appropriate addition to acute outpatient management?
- A. Oral theophylline
 - B.** Oral corticosteroids
 - C. An oral beta2-adrenergic agonist
 - D. Inhaled cromolyn
 - E. Inhaled corticosteroids
27. The parents of an 8 year old girl with asthma, atopic dermatitis and positive skin tests to dust mites, tree and grass pollens asked you about the likelihood that she will outgrow her asthma. What is the BEST response?
- A. Less than 20% of children with asthma outgrow symptoms by adulthood.
 - B.** Children with asthma and multiple inhalant allergies are less likely to outgrow asthma than children with asthma alone.
 - C. Children with exercise induced asthma rarely outgrow asthma.
 - D. Children with asthma & atopic dermatitis are more likely to outgrow asthma than children with asthma alone.
 - E. You cannot predict if she will outgrow asthma.
28. A 3-year-old child is brought to the emergency department with a barking cough, a hoarse voice, and mild stridor. You diagnose acute laryngotracheitis.

Which one of the following treatments in the emergency department will reduce this child's chance of subsequent hospitalization during this acute illness?

- A.** Dexamethasone (Decadron)
- B. Ceftriaxone (Rocephin)
- C. Azithromycin (Zithromax)
- D. 2.5% racemic epinephrine
- E. Placement in a mist tent

29. A 5-month-old infant has had several episodes of wheezing, not clearly related to colds. The delivery was normal; the infant received phototherapy for 1 day for hyperbilirubinemia. There is no strong family history of asthma. He spits up small amounts of formula several times a day, but otherwise appears well. His growth curve is normal. An examination is notable for mild wheezing. Which one of the following is the most likely?

- A. Benign reactive airway disease of infancy
- B. Cystic fibrosis
- C. Unresolved respiratory syncytial virus infection
- D. Early asthma
- E.** Gastroesophageal reflux

Explanation: Gastroesophageal reflux is a common cause of wheezing in infants. At 5 months of age, most infants are not continuing to spit up several times a day, and this is a major clue that the wheezing may be from the reflux. Also, there is no family history of asthma and the wheezing is not related to infections. Cystic fibrosis is more likely to present with recurrent infections and failure to thrive than with intermittent wheezing.

30. The rash most closely associated with celiac disease (gluten-sensitive enteropathy) is:

- A. Atopic dermatitis.
- B. Erythema marginatum.
- C. Erythema multiforme.
- D. Pyoderma gangrenosum.
- E.** Dermatitis herpetiformis

Done by: Rafeef Al-Qawasmeh

Rheumatology

Sources: Nelson textbook, Nelson essentials, and Kaplan

You can find Kawasaki disease and rheumatic fever lectures in Cardiology section

Organized by: Rafeef Qawasmeh

Juvenile idiopathic arthritis (JIA)

It is an idiopathic synovitis of peripheral joints associated with soft tissue swelling and joint effusion. It is the most common rheumatic disease in children and one of the more common chronic illnesses of childhood.

There is no sex predominance in systemic JIA (sJIA), but more girls than boys are affected in both oligoarticular (3 : 1) and polyarticular (5 : 1) JIA.

Pathophysiology:

- ☒ Both immunogenetic susceptibility and an external trigger are considered necessary.
- ☒ It is an autoimmune disease associated with alterations in both humoral and cell-mediated immunity. T lymphocytes have a central role, releasing pro-inflammatory cytokines favoring a type 1 helper T-lymphocyte response. Systemic JIA is characterized by dysregulation of the innate immune system with a lack of autoreactive T cells and autoantibodies. It therefore may be more accurately classified as an autoinflammatory disorder.
- ☒ Vascular endothelial hyperplasia and progressive erosion of articular cartilage and contiguous bone.
- ☒ DR8 and DR5 play a role.

Clinical manifestations

- ☒ Arthritis must be present to make a diagnosis of any JIA subtype.
- ☒ Morning stiffness with a limp or gelling after inactivity.
- ☒ Easy fatigability and poor sleep quality.
- ☒ Involved joints are often swollen, warm to touch, and painful on movement or palpation with reduced range of motion, but usually no redness.
- ☒ Arthritis in large joints, especially knees, initially accelerates linear growth and causes the affected limb to be longer, resulting in a discrepancy in limb lengths.
- ☒ Rapid and premature closure of the growth plate, resulting in shortened bones.

Criteria for diagnosis

- ☒ Age of onset < 16 years.
- ☒ Arthritis in 1 or more joints.
- ☒ Duration of disease: ≥6 weeks.
- ☒ Onset type defined by type of articular involvement in the 1st 6 months.
- ☒ Exclusion of other forms of arthritis, other connective tissue diseases and vasculitides, Lyme disease, psoriatic disease, IBD.

Categories of the disease (3 subtypes of onset)

1. Pauciarticular onset (oligoarticular):

- Fewer than 5 joints.
- The most common.
- Joints of lower extremity (hip never the presenting joint); isolated involvement of upper extremity large joints is less common.
- The arthritis is found in medium-sized to large joints; the knee is the most common joint involved, followed by the ankle and the wrist.
- Those in whom disease never develops in more than 4 joints are regarded as having persistent oligoarticular JIA, whereas evolution of disease in more than 4 joints after 6 months changes the classification to extended oligoarticular JIA.
- ANA positive → increased risk for asymptomatic anterior uveitis → periodic slit-lamp examination.
- ANA positivity may also be correlated with younger age at disease onset, female sex, asymmetric arthritis, and lower number of involved joints over time.

2. Polyarticular onset:

- Inflammation of ≥ 5 joints in both upper and lower extremities within the first 6 months of diagnosis.
- Children tend to have symmetric arthritis, which can affect any joint but typically involves the small joints of the hands, feet, ankles, wrists, and knees.
- Positive rheumatoid factor (RF+) – typically with onset of disease in an older child and with development of rheumatoid nodules.
- Rheumatoid nodules on the extensor surfaces of the elbows, spine, and over the Achilles tendons, although unusual, are associated with a more severe course and almost exclusively occur in RF-positive individuals.
- In contrast to oligoarticular JIA, it can present with evidence of systemic inflammation, including malaise, low-grade fever, growth retardation, anemia of chronic disease, and elevated markers of inflammation.
- Both large and small joints; resembles presentation in adults.
- May have cervical spine involvement (fusion of C1-4 may occur, and atlantoaxial subluxation may be demonstrable).
- Microganthia.
- Hip disease may be subtle.

3. Systemic onset:

- It is characterized by arthritis, fever, rash, and prominent visceral involvement, including hepatosplenomegaly, lymphadenopathy, and serositis (pericarditis).
- The characteristic fever, defined as spiking temperatures to $\geq 39^{\circ}\text{C}$ (102.2°F), occurs on a daily or twice-daily basis for at least 2 weeks, with a rapid return to normal or subnormal temperatures.
- Characteristic salmon-colored evanescent rash (linear or circular) mostly on trunk and proximal extremities. The classic rash is nonpruritic and migratory with lesions lasting < 1 hr.
- Koebner phenomenon is often present.
- Macrophage activation syndrome (MAS) is a rare but potentially fatal complication.
- Laboratory findings show the inflammation, with elevated ESR, CRP, WBC count, and platelet counts and anemia. The arthritis of JIA follows the systemic inflammation by 6 weeks to 6 months.

Laboratory and imaging studies

- ☒ Children with polyarticular and systemic-onset disease commonly show elevated acute phase reactants and anemia of chronic disease.
- ☒ Increased ANA in 40 – 85%, mostly with poly- and pauciarticular disease.
- ☒ A complete blood count should be performed to exclude leukemia, which also can present with limb pain.
- ☒ Older children and adolescents with polyarticular disease should have a rheumatoid factor performed.
- ☒ The most common radiologic finding in the early stages of JIA is a normal bone x-ray. Over time, periarticular osteopenia, resulting from decreased mineralization, is most commonly found.

Treatment

- ☒ Most with pauciarticular disease respond to NSAIDs alone.
- ☒ A minority of patients with oligoarthritis show no response to NSAIDs and injections, and therefore require treatment with disease-modifying antirheumatic drugs (DMARDs), methotrexate, and, if no response, TNF inhibitors.
- ☒ Those who have no or partial response after 4-6 weeks of treatment with NSAIDs or who have functional limitations, such as joint contracture or leg-length discrepancy, benefit from injection of intraarticular corticosteroids.
- ☒ Systemic steroids are recommended only for management of severe systemic illness, for bridge therapy during the wait for therapeutic response to a DMARD, and for control of uveitis.

- ☒ Ophthalmology follow up; physical therapy and occupational therapy.

Prognosis

- ☒ The prognosis of JIA is excellent, with an overall 85% complete remission rate.
- ☒ Children with oligoarticular JIA uniformly tend to do well, whereas children with polyarticular disease and systemic-onset disease constitute most children with functional disability.
- ☒ Children with oligoarthritis, particularly girls who are ANA-positive and with onset of arthritis earlier than 6 years of age are at greatest risk for development of chronic uveitis.
- ☒ There is no association between the activity or severity of arthritis and uveitis.
- ☒ Disease involving the hip and hand and wrist is also associated with a poorer prognosis and may lead to significant functional impairment.

Systemic lupus erythematosus (SLE)

It is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens.

Childhood SLE is rare before 5 years of age and is usually diagnosed in adolescence, with a median age at diagnosis of 11-12 years.

SLE predominantly affects females, with reported 2-5 : 1 ratio prior to puberty.

Etiology and pathogenesis

- ☒ A genetic predisposition to SLE is suggested by the association with congenital deficiencies of C1q, C2, and C4, as well as HLA-B8, HLA-DR2, and HLA-DR3.
- ☒ A hallmark of SLE is the generation of autoantibodies directed against self-antigens, particularly nucleic acids. These antibodies form immune complexes that become trapped in the microvasculature, leading to inflammation and ischemia.
- ☒ Certain viral infections (including EBV) may play a role in susceptible individuals.
- ☒ UV light exposure is known to aggravate SLE disease activity.
- ☒ Some are drug-induced, especially with anticonvulsants, sulfonamides, and antiarrhythmics.

Clinical presentation

- ☒ The most common presenting complaints of children with SLE include fever, fatigue, hematologic abnormalities, arthralgia, and arthritis.
- ☒ Arthritis is usually present in the 1st year of diagnosis, may be asymptomatic (morning stiffness, painless swelling) but is often a symmetric polyarthritis affecting large and small joints.
- ☒ Skin: malar rash, discoid lesions, livedo reticularis, photosensitivity, purpura and Raynaud phenomenon.
- ☒ Renal: glomerulonephritis, nephrotic syndrome, hypertension and renal failure. Renal disease is often asymptomatic underscoring the need for careful monitoring of blood pressure and urinalyses.
- ☒ CVS: pericarditis, Libman-Sacks endocarditis, cardiomegaly, heart failure.
- ☒ Neurologic: seizures, stroke, aseptic meningitis, chorea, psychiatric changes.
- ☒ Pulmonary: pleuritic pain, pulmonary hemorrhage.
- ☒ Hematologic: Coombs-positive hemolytic anemia, anemia of chronic disease, thrombocytopenia, leukopenia.
- ☒ Serositis: pleural, pericardial and peritoneal often with hepatosplenomegaly and lymphadenopathy.

- ☒ GI vasculitis: pain, diarrhea, bleeding and hepatitis.
- ☒ Antiphospholipid syndrome: arterial and venous thromboses, recurrent fetal loss, livedo reticularis, Raynaud phenomenon. It can be associated with lupus anticoagulant.

Diagnosis

Presence of 4 of the 11 American College of Rheumatology (ACR) criteria for SLE simultaneously or cumulatively over time establishes the diagnosis of SLE.

1. Malar rash.
2. Discoid rash.
3. Photosensitivity.
4. Oral or nasal ulcers.
5. Arthritis: nonerosive, ≥ 2 joints.
6. Serositis: pleuritis, pericarditis or peritonitis.
7. Renal manifestations: consistent renal biopsy, persistent proteinuria or renal casts.
8. Seizure or psychosis.
9. Hematologic manifestations: hemolytic anemia, leukopenia ($< 4,000$ leukocytes/ mm^3), lymphopenia ($< 1,500$ leukocytes/ mm^3), thrombocytopenia ($< 100,000$ thrombocytes/ mm^3).
10. Immunologic abnormalities: positive anti-dsDNA or anti-Smith antibody, false-positive rapid plasma regain test result, positive lupus anticoagulant test result, or elevated anticardiolipin immunoglobulin (Ig) G or IgM antibody.
11. Positive ANA.

Laboratory findings

- ☒ A positive ANA test result is present in 95-99% of individuals with SLE (good sensitivity) but has poor specificity. It is used for screening.
- ☒ Best test: anti-dsDNA (more specific; reflects disease activity).
- ☒ Anti-smith antibodies: specific for SLE but doesn't reflect disease activity.
- ☒ Serum levels of total hemolytic complement (CH50), C3, and C4 are typically decreased in active disease and often improve with treatment.
- ☒ Hypergammaglobulinemia is a common but nonspecific finding.

Treatment

- ☒ For all patients, sunscreen and avoidance of prolonged direct sun exposure and other ultraviolet light may help control disease.
- ☒ Hydroxychloroquine is recommended for all individuals with SLE if tolerated. It is used not only for the treatment of lupus skin disease, such as discoid lupus, but as maintenance therapy.

- ☒ NSAIDs can be useful for management of arthralgias and arthritis if no renal disease.
- ☒ Corticosteroids are a mainstay for treatment of significant manifestations of SLE.
- ☒ For patients who are not able to tolerate the tapering of corticosteroids, the use of steroid-sparing agents, such as azathioprine, methotrexate, or mycophenolate mofetil, may be indicated.
- ☒ Cyclophosphamide for severe disease.
- ☒ Patients with thrombosis and antiphospholipid syndrome should receive anticoagulation (use heparin during pregnancy).

Complications

- ☒ Within the 1st several years of diagnosis, the most common causes of death in individuals with SLE include infection and complications of glomerulonephritis and neuropsychiatric disease.
- ☒ Over the long-term, the most common causes of mortality also include complications of atherosclerosis and malignancy.
- ☒ Vascular necrosis secondary to corticosteroid use.

Juvenile dermatomyositis

It is the most common inflammatory myositis in children, distinguished by **proximal muscle weakness** and a characteristic rash.

It is characterized by activation of T and B lymphocytes, leading to vasculitis affecting small vessels of skeletal muscle, with immune complex deposition and subsequent inflammation of blood vessels and muscle.

The etiology of JDM is multifactorial, based on genetic predisposition and an unknown environmental trigger.

It can occur in all age groups with a peak incidence between 4 to 10 years. The disease is slightly more common in girls than boys.

Diagnostic criteria

Classic rash: (Heliotrope rash of the eyelids/ Gottron papules) plus 3 of following:

- ☒ Weakness: Symmetric/ Proximal.
- ☒ Muscle enzyme elevation (≥ 1): Creatine kinase/ Aspartate aminotransferase/ Lactate dehydrogenase/ Aldolase.
- ☒ Electromyographic changes: Short, small polyphasic motor unit potentials/ Fibrillations/ Positive sharp waves/ Insertional irritability/ Bizarre, high-frequency repetitive discharges.
- ☒ Muscle biopsy: Necrosis/ Inflammation.

Clinical manifestations

- ☒ The muscle disease of JDM primarily affects the proximal muscles, particularly the hip and shoulder girdles, and the abdominal and neck muscles.
- ☒ Children often exhibit extreme photosensitivity to ultraviolet light exposure with generalized erythema in sun-exposed areas. If seen over the chest and neck, this erythema is known as the “**shawl sign.**”
- ☒ The characteristic **heliotrope rash** is a blue-violet discoloration of the eyelids that may be associated with periorbital edema.
- ☒ **Gower sign** may be positive.
- ☒ Classic **Gottron papules** are bright pink or pale, shiny, thickened or atrophic plaques over the proximal interphalangeal joints and distal interphalangeal joints and occasionally on the knees, elbows, small joints of the toes, and ankle malleoli.

- ☒ Rarely, a thickened erythematous and scaly rash develops in children over the palms (known as **mechanic's hands**) and soles along the flexor tendons, which is associated with anti-Jo-1 antibodies.
- ☒ Patients may have periungual erythema and dilated nail-fold capillaries.
- ☒ Esophageal and respiratory muscles are also affected, resulting in aspiration or respiratory failure.
- ☒ Lipodystrophy and calcinosis are thought to be associated with long-standing or undertreated disease.
- ☒ Raynaud phenomenon, hepatomegaly, and splenomegaly may also occur.
- ☒ Some children present with classic rash but no apparent muscle weakness or inflammation; this variation is called amyopathic JDM or dermatomyositis sine myositis.

Laboratory and imaging studies

- ☒ Diagnosis is often delayed because of the insidious nature of disease onset.
- ☒ Many patients with JDM have no evidence of systemic inflammation (normal blood count and erythrocyte sedimentation rate).
- ☒ MRI is a noninvasive means of showing muscle inflammation.
- ☒ Elevated serum levels of muscle-derived enzymes (creatine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase).
- ☒ There may be anemia consistent with chronic disease.
- ☒ Antinuclear antibody is present in >80%
- ☒ Calcinosis is seen easily on radiographs, along the fascial planes and within muscles.

Differential diagnosis

If the presenting complaint is solely weakness without rash or atypical disease, other causes of myopathy should be considered:

- ☒ Polymyositis, infection-related myositis (influenza A and B, coxsackievirus B, and other viral illnesses).
- ☒ Muscular dystrophies (Duchenne and Becker as well as others).
- ☒ Myasthenia gravis, Guillain-Barré syndrome.
- ☒ Endocrinopathies (hyperthyroidism, hypothyroidism, Cushing syndrome, Addison disease, parathyroid disorders).
- ☒ Mitochondrial myopathies and metabolic disorders (glycogen and lipid storage diseases).
- ☒ Infections associated with prominent muscular symptoms include trichinosis, Bartonella infection, toxoplasmosis, and staphylococcal pyomyositis.

Myositis in children may also be associated with vaccinations, drugs, growth hormone, and graft-versus-host disease.

The rash of JDM may be confused with eczema, dyshidrosis, psoriasis, malar rash from systemic lupus erythematosus, capillary telangiectasias from Raynaud phenomenon, and other rheumatic diseases.

Muscle inflammation is also seen in children with SLE, JIA, mixed connective tissue disease, IBD, and antineutrophil cytoplasmic antibody–positive vasculitides.

Blunt trauma and crush injuries may lead to transient rhabdomyolysis with myoglobinuria.

Treatment

- ☒ Corticosteroids have altered the course of disease, lowering morbidity and mortality (the mainstay of treatment).
- ☒ Methotrexate decreases the length of treatment with corticosteroids, thereby reducing morbidity from steroid toxicity.
- ☒ Intravenous gammaglobulin is frequently used as an adjunct for treatment of severe disease.
- ☒ In a clinically stable child without debilitating weakness, oral prednisone at 2 mg/kg/ day (maximum 60 mg daily) is usually started.
- ☒ Hydroxychloroquine has little toxicity risk and is used as a secondary disease-modifying agent to reduce rash and maintain remission.
- ☒ Other medications for severe unresponsive disease include intravenous immunoglobulin, mycophenolate mofetil, cyclosporine, and cyclophosphamide.
- ☒ Patients should be advised to wear sun block and refrain from prolonged sun exposure. Accordingly supplementation with calcium and active forms of vitamin D is also indicated.
- ☒ Physical therapy and occupational therapy are integral parts of the treatment program.
- ☒ Bed rest is not indicated, because weight bearing improves bone density and prevents contractures.

Complications

- ☒ The most serious complication of JDM is the development of calcinosis.
- ☒ Patients with JDM who develop vasculitis also are at risk for gastrointestinal perforation and gastrointestinal bleeding.
- ☒ Lipoatrophy and insulin resistance, which can progress to type 2 diabetes.

Scleroderma and Raynaud phenomenon

Juvenile scleroderma is divided into 2 major categories, juvenile localized scleroderma (morphea), which is largely limited to the skin, and juvenile systemic sclerosis (JSSc), with multisystem organ involvement.

Children with localized disease often have a positive ANA test result, and some have antihistone antibodies. Children with systemic disease have higher rates of ANA positivity and may have anti-Scl 70 antibody (antitopoisomerase I).

Localized scleroderma

- ☒ The onset of scleroderma is generally insidious.
- ☒ The initial skin manifestations of localized disease usually include erythema or a bluish hue seen around an area of waxy induration; subtle erythema may be the only presenting sign.
- ☒ Edema and erythema are followed by indurated, hypopigmented or hyperpigmented, atrophic lesions.
- ☒ Patients sometimes present with arthralgias, synovitis, or flexion contractures.
- ☒ Limb length discrepancies as a result of growth impairment caused by involvement of muscle and bone.
- ☒ Children with "en coup de sabre" subtype may have symptoms unique to central nervous system involvement, such as seizures, hemifacial atrophy, ipsilateral uveitis, and learning/behavioral changes.

Systemic scleroderma

- ☒ Insidious onset with a prolonged course characterized by periods of remission and exacerbation, ending in either remission or, more commonly, chronic disability and death.
- ☒ The skin manifestations include an early phase of edema that spreads proximally from the dorsum of the hands and fingers and includes the face.
- ☒ As lesions spread proximally, flexion contractures develop at the elbows, hips, and knees associated with secondary muscle weakness and atrophy.
- ☒ Small oral stoma with decreased mouth aperture.
- ☒ Severe Raynaud phenomenon.
- ☒ Sclerodactyly.
- ☒ Resorption of the distal tufts of the distal phalanges may occur (acroosteolysis).
- ☒ Salt-and-pepper appearance of skin.
- ☒ Pulmonary disease is the most common visceral manifestation.

- ☒ Pulmonary arterial hypertension is a poor prognostic sign, developing either as a consequence of lung disease or independently as part of the vasculopathy.
- ☒ Other organ systems include gastrointestinal tract disease, renal arterial disease, and cardiac fibrosis. Mortality is most commonly a result of cardiopulmonary disease.

Raynaud Phenomenon

- ☒ It is the most frequent initial symptom in pediatric systemic sclerosis.
- ☒ It refers to the classic tri-phasic sequence of blanching, cyanosis, and erythema of the digits induced by cold exposure and/or emotional stress.
- ☒ It is most commonly independent of an underlying rheumatic disease (Raynaud disease).

Treatment

- ☒ Superficial morphea may benefit from topical corticosteroids or ultraviolet therapy. For lesions involving deeper structures, systemic therapy is recommended.
- ☒ A combination of methotrexate and corticosteroids is effective in treating the localized disease.
- ☒ Raynaud phenomenon RP is treated with cold avoidance and pharmacologic interventions are reserved for severe disease. Calcium channel blockers are the most common pharmacologic interventions. Others are losartan, prazosin, bosentan, and sildenafil.
- ☒ Angiotensin-converting enzyme inhibitors (captopril, enalapril) are recommended for hypertension associated with renal disease. Methotrexate or mycophenolate mofetil may be beneficial for skin manifestations. Cyclophosphamide and mycophenolate mofetil are used to treat pulmonary alveolitis and prevent fibrosis.

Familial Mediterranean fever (FMF)

Sources: Dr. Loay Al-Nouri seminar notes and Nelson textbook.

It is an autosomal recessive autoinflammatory disease, caused by mutations in MEFV gene on short arm of chromosome 16 encoding pyrin protein. Pyrin is expressed in granulocytes, monocytes, and dendritic cells, and in peritoneal, synovial, and dermal fibroblasts.

- ☒ There is a deficient activity of a C5a/interleukin (IL)-8 inhibitor.
- ☒ Old names for the disease: periodic fever/ aseptic peritonitis.

Ethnicity

- ☒ Gene distribution is mainly in Mediterranean region, hence the name.
- ☒ Most commonly Jews, Turks, Armenians, Arabs, and Italians.
- ☒ It is known as Armenian disease due to high incidence in Armenia.

Most patients present with symptoms in childhood, with 90% of patients presenting prior to the age of 20 yr.

Clinical manifestations

- ☒ It is characterized by suddenly appearing fever that lasts for 2 – 3 days and then suddenly disappears; this fever comes in periodic pattern. (Recurrent self-limited episodes).
- ☒ Peritonitis that can resemble acute abdomen.
- ☒ Pleuritic chest pain that is typically unilateral.
- ☒ Arthritis that occurs primarily in the large joints and may be accompanied by large, neutrophil-rich effusions, and is usually nonerosive and nondestructive.
- ☒ The hallmark cutaneous finding is an erysipeloid erythematous rash that overlies the ankle or dorsum of the foot.
- ☒ Other clinical findings include scrotal pain caused by inflammation of the tunica vaginalis testis, febrile myalgia, exercise induced myalgia (particularly common in children).
- ☒ Association with various forms of vasculitis, including Henoch-Schönlein purpura.
- ☒ The attack frequency can vary from weekly to 1-2 flares/year.

Diagnosis

- ☒ It is clinical-based. Labs are not very helpful.
- ☒ The differential diagnosis includes other hereditary periodic fever syndromes, and, depending on the specific circumstances, may include PFAPA, systemic-onset juvenile idiopathic arthritis (Still disease), cyclic hematopoiesis,

gynecologic disorders (when abdominal pain predominates), porphyria, hereditary angioedema, septic arthritis, and the crystalline arthritides.

- ☒ Genetic testing can be used as adjunctive evidence in ambiguous cases, and in circumstances in which the clinician has little experience with FMF or related conditions.

Treatment

- ☒ The main treatment is colchicine.
- ☒ 1 tablet = 0.5 mg
- ☒ The recommended dose is 0.5 mg/day (1 tablet) for children <5 years of age, 1 mg/day (2 tablets) for children between 5 and 10 years of age, and 1.5mg/day (3 tabs) for children >10 years.
- ☒ Side effects of colchicine: it is generally safe, but may cause gastroenteritis symptoms/ neuropathies (very rare).

Complications

- ☒ Amyloidosis is the most serious complication.
- ☒ The most common presenting sign of AA amyloidosis is proteinuria.
- ☒ Risk factors for the development of amyloidosis in FMF include homozygosity for the M694V MEFV mutation, polymorphisms of the serum AA gene (encoding AA), noncompliance with colchicine treatment, male gender, and a positive family history of AA amyloid.

Henoch-Schönlein Purpura (HSP)

It is the most common vasculitis of childhood and is characterized by leukocytoclastic vasculitis and **IgA deposition** in the small vessels in the skin, joints, gastrointestinal tract, and kidney. It is the most common cause of **nonthrombocytopenic purpura** in children.

In all tissues, immunofluorescence identifies IgA deposition in walls of small vessels, accompanied to a lesser extent by deposition of C3, fibrin, and IgM.

Children usually between the ages of 3 and 10 yr. it is more common in males.

It is more common in the winter and spring, and is unusual in summer months. Many cases of HSP follow a documented upper respiratory infection.

Clinical manifestations

- ☒ The hallmark of HSP is its rash: palpable purpura starting as pink macules or wheals and developing into petechiae, raised purpura, or larger ecchymoses.
- ☒ The skin lesions are usually symmetric and occur in gravity-dependent areas (lower extremities) or on pressure points (buttocks).
- ☒ Low grade fever and fatigue.
- ☒ Musculoskeletal involvement, including arthritis and arthralgias, is common. The arthritis tends to be self-limited and oligoarticular, with a predilection for the lower extremities, and does not lead to deformities.
- ☒ GI manifestations include abdominal pain, vomiting, diarrhea, paralytic ileus and melena; intussusception, mesenteric ischemia, intestinal perforation are uncommon.
- ☒ Renal involvement occurs in up to 50%, manifesting as microscopic hematuria, proteinuria, hypertension, frank nephritis, nephrotic syndrome, and acute or chronic renal failure.
- ☒ Hepatosplenomegaly, lymphadenopathy.
- ☒ Neurologic manifestations may also occur. They include intracerebral hemorrhage, seizures, headaches, and behavior changes.

Diagnosis and laboratory findings

- ☒ The diagnosis of HSP is a clinical one and is often straightforward when the typical rash is present.
- ☒ Common but nonspecific findings include leukocytosis, thrombocytosis, mild anemia, and elevations of ESR and CRP.
- ☒ Increased IgA, IgM
- ☒ May have anticardiolipin or antiphospholipid antibodies.
- ☒ Occult blood is frequently found in stool specimens.

- ☒ The diagnosis of HSP is based on the presence of two of four criteria:
 - ✓ Palpable purpura - Raised, palpable hemorrhagic skin lesions in the absence of thrombocytopenia.
 - ✓ Bowel angina - Diffuse abdominal pain or the diagnosis of bowel ischemia.
 - ✓ Diagnostic biopsy - Histologic changes showing granulocytes in the walls of arterioles or venules; IgA deposits in vessel wall.
 - ✓ Pediatric age group Age <20 years at onset of symptoms.

Treatment

- ☒ Treatment for mild and self-limited HSP is supportive, with an emphasis on assuring adequate hydration, nutrition, and analgesia.
- ☒ A short-term course of nonsteroidal anti-inflammatory drugs can be administered for the acute arthritis.
- ☒ Systemic corticosteroids usually are reserved for children with gastrointestinal disease and provide significant relief of abdominal pain.
- ☒ Acute nephritis typically is treated with corticosteroids but may require more aggressive immunosuppressive therapy.

Complications

- ☒ Most cases of HSP are monophasic, lasting 3 to 4 weeks and resolving completely. The rash can wax and wane, however, for 1 year after HSP.
- ☒ Acutely, serious gastrointestinal involvement such as intestinal perforation imparts significant morbidity and mortality.
- ☒ Renal disease is the major long-term complication.

The END

Sources: Nelson textbook, Nelson essentials, and Kaplan

You can find Kawasaki disease and rheumatic fever lectures in Cardiology section

Rafeef Qawasmeh

Genetic & Metabolic Disorders

General rules of genetics (source: Nelson essential)

Rules of Autosomal Dominant Inheritance

Trait appears in every generation

Each child of an affected parent has a one in two chance of being affected

Males and females are equally affected

Male-to-male transmission occurs

Traits generally involve mutations in genes that code for regulatory or structural proteins (collagen)

Rules of Autosomal Recessive Inheritance

Trait appears in siblings, not in their parents or their offspring

On average, 25% of siblings of the proband are affected (at the time of conception, each sibling has a 25% chance of being affected)

A *normal* sibling of an affected individual has a two-thirds chance of being a carrier (heterozygote)

Males and females are likely to be affected equally

Rare traits are likely to be associated with parental consanguinity

Traits generally involve mutations in genes that code for enzymes (e.g., phenylalanine hydroxylase-deficient in PKU) and are associated with serious illness and shortened life span

Rules of X-Linked Recessive Inheritance

Incidence of the trait is higher in males than in females

Trait is passed from carrier females, who may show mild expression of the gene, to half of their sons, who are more severely affected

Each son of a carrier female has a one in two chance of being affected

Trait is transmitted from affected males to all their daughters; it is never transmitted father to son

Because the trait can be passed through multiple carrier females, it may *skip* generations

Unusual patterns of inheritance

Mitochondrial Inheritance

Human cells contain nonnuclear DNA; a single chromosome is present in each mitochondrion, and mutations within this DNA are associated with a group of diseases.

Mitochondrial DNA (mtDNA), which is circular and 16.5 kb in length, replicate independently of nuclear DNA. Involved in energy production used to run the cell, mtDNA codes for a few respiratory chain proteins (most mitochondrial proteins are coded on **nuclear** DNA) and for a set of transfer RNAs unique to mitochondrial protein synthesis. Virtually all mitochondria are supplied by the oocyte, which means that mtDNA is maternally derived. A woman with a mutation in mtDNA passes this mutation to all her children. More than one population of mitochondria may be present in the oocyte, a phenomenon called **heteroplasmy**. The mtDNA mutation may be present in a few or many mitochondria. When the fertilized egg divides, mitochondria are distributed randomly. The presence of symptoms in the offspring, and their severity, depends on the ratio of mutant to wild-type mtDNA present in a particular tissue. If an abundance of mutant mitochondria exists in tissue that has high energy requirements (brain, muscle, and liver), clinical symptoms occur. If fewer mutant mitochondria are present, few clinical symptoms may be seen.

Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS) is an example of a mitochondrial disorder. Normal in early childhood, individuals affected with MELAS develop episodic vomiting, seizures, and recurrent cerebral insults that resemble strokes between 5 and 10 years of age. In 80% of cases, analysis of the mtDNA reveals a specific mutation

(A3242G) in *MTTL1*, a gene that codes for a mitochondrial transfer RNA.

In families in which MELAS occurs, a range of symptoms is seen in first-degree relatives, including **progressive external ophthalmoplegia**, hearing loss, cardiomyopathy, and diabetes mellitus. Although all offspring of a woman who carries a mutation would be affected, because of heteroplasmy the severity of disease varies depending on the percentage of mitochondria bearing the mutation that are present.

Uniparental Disomy

Evaluation of a child with uniparental disomy (UPD) reveals a normal karyotype. However, chromosomal markers for one particular chromosome are identical to the markers found on the chromosomes of the patient's mother or father (but not both as is normal). In UPD, the individual inherits two copies of one parent's chromosome and no copy from the other parent.

UPD probably occurs through a few mechanisms, but the most common results from a spontaneous *rescue* mechanism. At the time of conception, through nondisjunction, the fertilized egg is trisomic for a particular chromosome, with two copies of one parent's chromosome and one copy of the other parent's chromosome; conceptuses with trisomy often miscarry early in development. Fetuses with UPD survive because they spontaneously lose one of three copies of the affected chromosome. If the single chromosome from one parent is lost, the patient has UPD.

An alternate explanation involves monosomy for a chromosome rather than trisomy. Had the conceptus, at the time of conception, inherited only a single copy of a chromosome, spontaneous duplication of the single chromosome would lead to UPD.

Expansion of a trinucleotide repeat

More than 50% of human DNA appears as repeat sequences, two or three bases repeated over and over again. Disorders caused by expansion of trinucleotide repeats include **fragile X syndrome (FRAX)**, **Huntington disease**, **myotonic dystrophy**, **Friedreich ataxia**, and the **spinocerebellar ataxias**. Although an increase in the number of the three repeated bases is at the heart of each disorder, the molecular mechanism differs.

Genetic & metabolic disorders

This sheet includes notes from Dr. Ali Hawamdeh seminars and some topics from Kaplan.

- Genetic disorders are common in Jordan, due to:
 1. High consanguinity rate.
 2. Screening and antenatal diagnosis not well-developed.
- AR is the most common pattern of inheritance.
- AR: recurrence risk in each pregnancy is 25% / AD: 50%
- No male to male inheritance in X-linked diseases.
- Mitochondrial inheritance: from the mother. (the sperm has its mitochondria in the tail which is not involved in fertilization) / The only cell that has no mitochondria is the erythrocyte.

AD	AR	X-linked
- Hereditary spherocytosis. - Heterochromia iridis. - Ehlers-Danlos syndrome. - Marfan syndrome. - Neurofibromatosis. - Tuberous sclerosis complex. - Noonan syndrome. - Achondroplasia.	- Glycogen storage disease. - Gaucher disease. - Ataxia telangiectasia. - Mucopolysaccharidosis except for type II. - Tyrosinemia type II. - Homocystinuria.	- anhidrotic ectodermal dysplasia. - Mucopolysaccharidosis II (hunter syndrome). - Fragile X syndrome.

Rickets

14 year-old girl referred from orthopedic clinic with genu varum. On examination: no teeth/ short stature. X-ray of hand showing cupping & fraying, osteopenia (active rickets). Investigations: normal calcium/ high alkaline phosphatase/ low phosphorus/ normal PTH.

- Diagnosis: vitamin D resistant type.
- Rickets: poor mineralization of growing bone due to lack of vitamin D, calcium or phosphorus.
- Alkaline phosphatase: the most sensitive marker.
- Types of rickets: vitamin D dependent type 1/ vitamin D dependent type 2/ vitamin D resistant type/ nutritional/ renal rickets.
- Vit D dependent type 1: lack of enzyme/ type 2: lack of receptor.
- Alopecia is present in 75% of Vit D dependent type 2 patients.
- Renal rickets: the only type in which phosphate is high.

- Renal osteodystrophy = 2ry hyperparathyroidism + rickets.
- Rachitic rosary + jaundice: think of rickets.

BIOCHEMICAL PROFILE

	Ca	P	PTH	ALP	25(OH) Vit D	
Vit D Deficiency	N/Low	N/Low	Increased	Increased	Low	Ur P-low
Vit D Dependent	Low	Low	Increased	Increased	Normal	
Vit D resistant	N/Low	Low	Normal	Increased		D3 –N Ur P-High
Renal Osteodystrophy	N/Low	Increased	Increased	Increased	Normal	D3- low

Glycogen storage disease

Lethargic infant with abdominal distention. Glucose test was done (the 1st to do in lethargic patient), revealed hypoglycemia. On examination: massive hepatomegaly, no splenomegaly. Urinalysis: ketone positive (exclude hyperinsulinemia).

- Diagnosis: glycogen storage disease.
- It is an AR.
- Treatment: uncooked cornstarch.
- Liver biopsy doesn't diagnose glycogen storage disease except if it was for enzyme assay.

Growth hormone deficiency

2 year-old boy with choppy cheeks and long eyelashes. Hypoglycemia/ micropenis/ apnea/ no hepatomegaly.

- Long eyelashes: sign of chronic disease.
- Diagnosis: growth hormone deficiency.
- He was treated as glycogen disease & given glucose: the cause of choppy cheeks.

Beckwith-wiedemann syndrome

Macroglossia / umbilical hernia/ salmon patches on face/ crease on ear/ hypoglycemia (due to hyperinsulinemia).

- Hyperinsulinemia due to pancreatic beta cell hyperplasia.
- Check insulin level at the peak of hypoglycemia.
- Glucose control is the most important initial management.
- Increased risk of abdominal tumors (Wilms)

Acrodermatitis enteropathica 2ry to zinc deficiency

Infant with NG tube/ skin rash on face, hands, feet & thighs/ alopecia/ diarrhea.

- No need for skin biopsy.
- Alkaline phosphatase is low because it is zinc dependent.

Langerhans cell histiocytosis

- Severe seborrheic dermatitis / pus from ear.
- Diagnosis by skin biopsy.

Acute pancreatitis due to hyperlipidemia

Severe abdominal pain / xanthoma on elbow/ Na = 125 (hyponatremia).

- Hyperlipidemia: 1ry (genetic causes) or 2ry (acquired).
- Nephrotic syndrome, liver disease, B-blocker and lack of exercise are causes of acquired hyperlipidemia.
- Hyponatremia:
 - ✓ May be due to hyperglycemia (DKA 2ry to acute pancreatitis).
 - ✓ Pseudo-hyponatremia is the main cause.
 - ✓ Na is extracellular, higher in bile/ potassium is higher in saliva.

Hereditary spherocytosis

4 y/o boy with gallbladder stones , bullae and scars on hands, hypopigmentation areas with line of demarcation (**photosensitive dermatitis**), skin lesions on face.

- Hereditary spherocytosis is severe hemolytic anemia/ AD.
- Peripheral blood in hemolysis: ↑ reticulocytes/ ↑ LDH/ ↑ indirect bilirubin/ ↓ hemoglobin/ ↓ haptoglobin).
- Urinalysis in hemolysis: hemoglobinuria/ excessive urobilinogen.

Epidermolysis bullosa

A group of inherited connective tissue diseases that cause blisters in the skin and mucosal membranes.

- Epidermolysis bullosa simplex (AD).
- Junctional epidermolysis bullosa (AR).
- Dystrophic epidermolysis bullosa (AR or AD).

Anhidrotic ectodermal dysplasia

Swollen lips/ black discoloration below eyes/ little hair on eyebrows/ teeth problems (big teeth)/ fever that is unresponsive to medications.

- The 1 question you have to ask: is the child able to sweat?
- " They have a reduced ability to sweat because they have fewer sweat glands than normal or their sweat glands do not function properly. Sweating is a major way that the body controls its temperature; as sweat evaporates from the skin, it cools the body. An inability to sweat can lead to a dangerously high body temperature (hyperthermia)".
- X-linked.
- Management: keep away from high temperatures/ special suits.

Hereditary sensory and autonomic neuropathy type IV

" It is a rare genetic disorder that usually begins in infancy and is characterized by an inability to feel pain and an inability to sweat (anhidrosis). Affected individuals also cannot feel temperature and cannot distinguish between hot and cold. The sensory loss in individuals with HSAN IV is due to abnormal functioning of the sensory nerves that control responses to pain and temperature. Anhidrosis can cause recurrent episodes of fever and high body temperature ".

Gaucher disease

3 y/o boy with abdominal distension and everted umbilicus. On examination, there was splenomegaly and hepatomegaly. CBC: pancytopenia.

- Features of hypersplenism (pancytopenia, active formation of the decreased element in the bone marrow, splenomegaly, and reversal of the symptoms by splenectomy).
- Abdominal distension causes: gaseous (celiac disease)/ fluid (ascites as in nephrotic syndrome)/ organomegaly (as in this case).
- Gaucher disease is the most common lysosomal storage disease.
- AR.

- It is a form of sphingolipidosis, as it involves dysfunctional metabolism of sphingolipids.
- The disorder is characterized by bruising, fatigue, anemia, low blood platelet count and enlargement of the liver and spleen.
- Caused by a hereditary deficiency of the enzyme glucocerebrosidase (also known as glucosylceramidase), which acts on glucocerebroside.
- Treatment: enzyme replacement therapy or bone marrow transplant. If unavailable, do splenectomy.

Niemann–Pick disease

Severe fragile limbs/ admitted with 1ry peritonitis. (1ry = no rupture or perforation).

- " It involves dysfunctional metabolism of sphingolipids, which are fats found in cell membranes, so it is a kind of sphingolipidosis. Sphingolipidoses, in turn, are included in the larger family of lysosomal storage diseases " .

Ataxia telangiectasia

Young girl presented with ataxia and telangiectasia in bulbar conjunctiva.

- AR.
- ↑ Alpha fetoprotein.
- Defect in DNA repair that is related to exposure to ionizing radiation.

Congenital glaucoma

2 y/o child presented with excessive lacrimation. On examination: megalocornea (>12 mm). Misdiagnosed as lacrimal duct obstruction. Later on, presented with photophobia and blepharospasm.

- Triad: epiphora (overflow of tears)/ photophobia/ blepharospasm.

Heterochromia iridis

- " It is of three kinds. In complete heterochromia, one iris is a different color from the other. In sectoral heterochromia, part of one iris is a different color from its remainder and finally in "central heterochromia" there are spikes of different colors radiating from the pupil. "
- AD.
- Might be a normal finding in healthy person. But it is considered abnormal if there were associated abnormal features e.g. deafness like in Waardenburg syndrome.

Alkaptonuria (black urine disease)

- The 1st discovered among metabolic diseases.
- Inherited genetic disorder in which the body cannot process the amino acids phenylalanine and tyrosine.
- " The body accumulates an intermediate substance called homogentisic acid in the blood and tissues. Homogentisic acid and its oxidated form *alkapton* are excreted in the urine, giving it an unusually dark color ".

Ehlers-Danlos syndrome

- Connective tissue disorder, AD
- Type I is the most common.
- Findings: droopy ears/ hyperextensible skin/ fragile skin/ poor wound healing/ joint hyperlaxity/ blue sclera/ myopia/ glaucoma/ ectopia lentis/ retinal detachment/ intracranial aneurysm/ aortic root dilatations.

Marfan syndrome

- AD, mutations in fibrillin gene (FBN1).
- Findings: tall stature with long, slim limbs and little fat/ arachnodactyly/ joint laxity with kyphoscoliosis/ pectus excavatum or carinatum.

Homocystinuria VS Marfan's syndrome

- inheritance:
 - Marfan's - autosomal dominant
 - homocystinuria - autosomal recessive
- lens dislocation:
 - Marfan's - upward lens dislocation
 - homocystinuria - downward lens dislocation
- aortic incompetence:
 - Marfan's - aortic incompetence may occur
 - homocystinuria - heart rarely affected
- intellectual development:
 - Marfan's - normal
 - homocystinuria - mental retardation

General notes

- cystinuria: renal stones.
- Cystinosis: corneal photophobia.
- 50% of bilateral congenital cataract: AD.
- **Coloboma of the iris** is a hole or defect of the iris of the eye. Most colobomas are present since birth (congenital). It can look like a second pupil or a black

notch at the edge of the pupil. This gives the pupil an irregular shape. It can also appear as a split in the iris from the pupil to the edge of the iris.

- **Brushfield spots – Down syndrome:** are small, white or grayish/brown spots on the periphery of the iris in the human eye due to aggregation of connective tissue, a normal iris element.
- **Cherry red spots** (lipid deposition) on macula considered normal, but around it is abnormal. These spots indicate lipid storage disease. Vision is not affected.
- **Café-au-lait spots on iris: neurofibromatosis type 1.**

Abetalipoproteinemia (Bassen-Kornzweig syndrome)

- Retinitis pigmentosa + chronic diarrhea + ataxia
- AR

Neurofibromatosis - AD

- Neurocutaneous syndrome.
- The hallmark of type 1: café-au-lait spots.
- Criteria for diagnosis of type 1: Clinical diagnosis requires the presence of at least 2 of 7 criteria. (from Medscape)
 - ✓ Six or more café-au-lait spots or hyperpigmented macules =5 mm in diameter in prepubertal children and 15 mm postpubertal.
 - ✓ Axillary or inguinal freckles (>2 freckles).
 - ✓ Two or more typical neurofibromas or one plexiform neurofibroma.
 - ✓ Optic nerve glioma.
 - ✓ Two or more iris hamartomas (Lisch nodules), often identified only through slit-lamp examination by an ophthalmologist.
 - ✓ Sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis.
 - ✓ First-degree relative (e.g. mother, father, sister, brother) with NF1.
- The hallmark of type 2: bilateral acoustic fibroma.

Tuberous sclerosis complex - AD

- Adenoma sebaceum (angiofibroma): looks like acne in mild form.
- Shagreen patches: Flesh coloured orange-peel connective tissue naevi of varying sizes, usually on the lower back.
- Ovoid or ash leaf-shaped white macules: hypopigmented/ must be at least 3 in number to make the diagnosis.
- Calcified tubercle (periventricular) – on CT (without contrast).
- Infantile spasm.

Sturge- Weber syndrome

- Port-wine stain hemangioma.
- Hemangioma affecting the trigeminal nerve divisions.
- If ophthalmic division was affected: high incidence of glaucoma.
- Not inherited.

General notes:

- Microcephaly = small brain.
- There is no treatable form of microcephaly.
- Craniosynostosis: abnormal closure of sutures.
- Lissencephaly: smooth brain (no gyri).

Hypomelanosis of Ito

- Associated with seizures.
- Christmas tree distribution over the back.
- Macular lesions → papular → vesicular.

Incontinentia pigmenti

- X-linked.
- Spontaneous abortion of male conceptus.
- Female presents with skin manifestations: (hypo and hyper pigmentation) / vesicles.

Mucopolysaccharidosis

- Lysosomal storage disease.
- Hypertrichosis.
- Widening of wrist.
- Coarse facial features.
- Raccoon eyes. (1st DDX is basal skull fracture).
- Most of them are AR except for Hunter syndrome (mucopolysaccharidosis II, X-linked).

Hunter syndrome

- Short stature.
- Skin nodules on back.
- Hepatosplenomegaly.

GM1 gangliosidosis

- Lysosomal storage disease.
- Excessive or extensive mangolion spots (also in hunter syndrome).
- Exophthalmos.
- Macrosomia.
- Large umbilical hernia.
- Hepatosplenomegaly.

Maple syrup urine disease

10 y/o wasted male, on diaper, behaves like an infant. Also, he has Hypertrichosis.

- Defect in leucine, isoleucine, and valine.
- There is a special milk and food for them.
- رائحة البول مثل السكر المحروق

Phenylketonuria

Developmental delay/ fair-skin unlike parents/ seizures.

- Similarity between patients.
- Treatment: restriction of protein intake but it is not contraindicated.
- If protein isn't given at all, phenylalanine deficiency may develop.
- The only contraindication of breast feeding in metabolic diseases is galactosemia.

Tyrosinemia type II

- Oculocutaneous tyrosinemia/ Richner-Hanhart syndrome.
- AR
- Hyperkeratosis of palms and soles.
- Photophobia.
- Good prognosis.

Down syndrome

- Trisomy 21.
- Not inherited.
- Most common cause of aneuploidy.
- Males are infertile.
- Females are fertile (50% of her children: Down).
- The risk increases with advancing maternal age.
- Duodenal atresia with bilious vomiting: common in Down syndrome. Do chromosomal analysis.

- Findings: Simian crease/ **Clinodactyly**: Curving of the fifth finger (the little finger) toward the fourth finger (the ring finger)/ upward slanting palpebral fissures/ brushfield spots/ inner epicanthal folds/ small stature/ mouth open with tongue protrusion/ short neck/ flat occiput/ hypotonia (muscle tone improves with age)/ hearing loss of any type/ cardiac anomalies/ hypothyroidism/ atlanto-axial instability/ acute lymphocytic leukemia/ mental retardation.
- Major cause for early mortality is congenital heart disease.

Trisomy 18 (Edwards syndrome)

- The risk increases with advanced maternal age.
- Findings: growth deficiency/ mental retardation/ low-set, malformed ears/ micrognathia/ microcephaly/ prominent occiput/ clenched hand/ short sternum/ cardiac anomalies/ Rocker-bottom feet/ hammer toe/ omphalocele.
- Most don't survive first year/ many spontaneous abortions.

Trisomy 13 (Patau syndrome)

- Defect of midface, eye, and forebrain development.
- Risk with older maternal age.
- Findings: holoprosencephaly and other CNS defects/ severe mental retardation/ microcephaly/ microphthalmia/ severe cleft lip, palate or both/ scalp defects in parietal-occipital area/ postaxial polydactyly/ single umbilical artery/ cardiac anomalies.

General notes:

- **Isolated polydactyly** is inherited as AD.
- **Postaxial polydactyly** is more associated with mental retardation than preaxial.
- Postaxial polydactyly: refers to polydactyly where the additional digit is on the ulnar margin of the hand, or lateral to the 5th toe.
- **Syndactyly** is a condition where in two or more digits are fused together. Most common site is between 2nd and 3rd toes.
- **Arachnodactyly**: spider fingers (long fingers) / as in Marfan syndrome.

Fragile X syndrome

- It is the most common cause of inherited mental retardation.
- It is a trinucleotide repeat disorder; others are Huntington, freidrieich ataxia and myotonic dystrophy.
- Fragile site on long arm of X in affected males and some carrier females.
- X-linked dominant.

- Findings: large ears/ dysmorphic facial features/ large jaw/ large face/ large testes/ normal lifespan.

Prader-Willi syndrome

- Extreme hypotonia at birth.
- 1st 6 months of life they are on NG tube because of feeding problems.
- After that, increased feeding (severe polyphagia) and weight gain plus slow height attainment (short stature).
- Deletion or inactivation of genes on the paternally inherited chromosome 15 while the maternal copy, which may be of normal sequence, is imprinted and therefore silenced.
- Findings: mild to severe mental retardation/ small hands and feet/ small genitalia/ hypothalamic-pituitary dysfunction/ hypogonadotropic hypogonadism/ decreased life expectancy relative to morbid obesity.

Angelman syndrome

- Findings: Developmental delay/ severe mental retardation/ absent speech or <6 words/ ataxia and jerky arm movements resembling a puppet's movements/ seizures.
- Frequent inappropriate laughter or smiling.
- Deletion or inactivation of genes on the maternally inherited chromosome 15 while the paternal copy, which may be of normal sequence, is imprinted and therefore silenced.

Macroorchidism

- A disorder found in males where a subject has abnormally large testes.
- The condition is commonly inherited in connection with fragile X syndrome.
- Big ears.
- Joint laxity.

Noonan syndrome

- Pectus excavatum (funnel chest).
- AD
- Webbing of the neck.
- Low hair line.
- Referred to as the male version of Turner's syndrome.
- Most common congenital heart disease is pulmonary stenosis.

Turner syndrome

- It is a condition in which a female is partly or completely missing an X chromosome (45, XO).
- Most common congenital heart disease is coarctation of aorta.
- Short and webbed neck, low-set ears, low hairline at the back of the neck, short stature, and swollen hands and feet are seen at birth.
- Congenital lymphedema (not in Noonan syndrome).
- Horseshoe kidney and other renal defects.
- No relation to maternal age. (Down syndrome and klinefelter syndrome have increased incidence with increased maternal age).
- Estrogen treatment is indicated.

Klinefelter syndrome (XXY)

- Most common findings manifested by puberty.
- Findings: mental retardation/ behavioral problems/ long limbs (arm span > height)/ slim/ gynecomastia/ hypogonadotropic hypogonadism.

Achondroplasia

- AD
- Common cause of dwarfism.
- Short stature/ waddling gait/ lordotic posture/ megaloccephaly/ small foramen magnum/ small cranial base/ prominent forehead/ small Eustachian tube (otitis media and hearing loss).
- Good mentality.
- Homozygous achondroplasia is incompatible with life.
- If both parents are normal, how could it be explained?
 - ✓ New mutation.
 - ✓ Variable penetrance.
 - ✓ ما يكون ابنهم

Osteogenesis imperfect

- Brittle bone disease.
- Blue sclera.
- Deficiency of type I collagen.

Potter syndrome

- The atypical physical appearance of a fetus or neonate due to oligohydramnios experienced in the uterus.
- Classic Potter sequence occurs when the developing fetus has bilateral renal agenesis.

- Potter faces (hypertelorism, epicanthal folds, low-set flattened ears, microgathia, compressed flat nose), clubbed feet, pulmonary hypoplasia and cranial anomalies related to the oligohydramnios.
-

Poland anomaly

- Rare birth defect characterized by underdevelopment or absence of the chest muscle (pectoralis) on one side of the body, and usually also webbing of the fingers (cutaneous syndactyly) of the hand on the same side.

Amniotic band syndrome

- Occurs when the fetus becomes entangled in fibrous string-like amniotic bands in the womb, restricting blood flow and affecting the baby's development.
- Can cause a number of different birth defects depending on which body part(s) is affected. If a band wraps tightly around a limb, the limb can actually be completely amputated. The baby may be born missing fingers, toes, part of an arm or leg.
- If the band is across the baby's face it can cause cleft lip and palate.
- Occurs randomly.

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Genetics

Neurology

Disease or syndrome	Mode of inheritance	Other
Dystrophia myotonica type I	dominantly inherited and caused by a nucleotide triplet repeat expansion, CTG in the DMPK gene,	anticipation through generations, especially when maternally transmitted
Friedreich ataxia	autosomal recessive .	triplet repeat in the FXN gene causing a lack of the frataxin protein
Ataxia telangiectasia	autosomal recessive.	disorder of DNA repair
Charcot-Marie-Tooth disease	CMT1A accounts for 70–80% and is inherited in an autosomal dominant manner in two thirds, one third developing the mutation de novo . The other types of CMT disease can be inherited by autosomal dominant, recessive or X-linked modes.	They are caused by mutations in myelin genes.
CADASIL	AD	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Neurofibromatosis type 1 (NF-1)	AD	AD, highly penetrant condition, with variable expression. mutation in the neurofibromin-1 (NF1) gene, which arises in about 50% as a de novo mutation
Neurofibromatosis type 2	AD	mutation in the NF2 gene, About 50% are due to de novo mutations
Tuberous sclerosis	AD	AD, with variable penetrance, and up to 70% of mutations arise de novo. mutation in the TSC1 or TSC2 genes.
Sturge–Weber syndrome	sporadic	
adrenoleukodystrophy	X-linked	
Retinoblastoma	AD	Incomplete penetrance
malignant hyperthermia	AD	

Development

Disease or syndrome	Mode of inheritance	Other
Fragile X syndrome	X-linked dominant	#expansion of the CGG triplet repeat within the Fragile X mental retardation 1 (FMR1) gene on the X chromosome. This results in not enough fragile X mental retardation protein (FMRP) #X-linked dominant condition with variable expressivity and possibly reduced penetrance.
Phenylketonuria	AR	

Rheumatology

Disease or syndrome	Mode of inheritance	Other
Familial Mediterranean fever (FMF)	AR	mutations in MEFV gene on short arm of chromosome 16 encoding pyrin protein

Respiratory

Disease or syndrome	Mode of inheritance	Other
Cystic fibrosis	AR	CF transmembrane conductance regulator (CFTR). chromosome 7. the most frequent mutation (about 78%) in the UK is $\Delta F508$

Hematology

Disease or syndrome	Mode of inheritance	Other
Hereditary spherocytosis	AD	25% is (de novo) with no family hx
Glucose-6-phosphate dehydrogenase deficiency	X-linked	More in males, occur in homozygous females but more commonly in females with lyonization
Sickle cell disease	AR	point mutation in codon 6 of the β -globin gene, which causes a change in the amino acid encoded from glutamine to valine
Diamond–Blackfan anemia (DBA)	AD	AD with incomplete penetrance
Fanconi anaemia	AR	mutations in one of the many FANC genes, most commonly FANCA.
Shwachman–Diamond syndrome	AR	SBDS gene mutation
haemophilia A	X-linked recessive	FVIII deficiency, $\frac{2}{3}$ with family hx & $\frac{1}{3}$ sporadic
haemophilia B	X-linked recessive	FIX deficiency, $\frac{2}{3}$ with family hx & $\frac{1}{3}$ sporadic
von Willebrand disease	AD	
Wiskott–Aldrich syndrome (WAS)	X-linked recessive	
Bernard–Soulier syndrome (BSS)	AR	
Proteins C and S and antithrombin deficiencies	AD	

Growth and puberty

Disease or syndrome	Mode of inheritance	Other
Noonan syndrome	AD	

Endocrine

Disease or syndrome	Mode of inheritance	Other
Maturity onset diabetes of the young" (MODY)	AD	
DiGeorge syndrome, also known as 22q11.2 deletion syndrome,	AD	
Congenital adrenal hyperplasia	AR	
5α-Reductase deficiency	AR	

Kidney and urinary tract disorders

Disease or syndrome	Mode of inheritance	Other
Congenital nephrotic syndrome	AR	
Alport syndrome	X-linked recessive	
autosomal recessive polycystic kidney disease	AR	
autosomal dominant adult-type polycystic kidney disease	AD	

GI

Disease or syndrome	Mode of inheritance	Other
Crigler-Najjar Syndrome <ul style="list-style-type: none"> • absent (type I) glucuronyl transferase 	AR	
Crigler-Najjar Syndrome <ul style="list-style-type: none"> • severely decreased (type II) glucuronyl transferase 	AD	

Alpha-1 antitrypsin deficiency.	autosomal co-dominant	one defective allele tends to result in milder disease than two defective alleles
Wilson disease	AR	
galactosemia	AR	

Immunology & allergy

Disease or syndrome	Mode of inheritance	Other
Leukocyte-adhesion deficiency	AR	
Wiskott–Aldrich syndrome (WAS)	X-linked recessive	WAS protein
Ataxia telangiectasia	AR	A-T mutation on chromosome 11 (11q22-23); protein kinase
X-linked agammaglobulinemia (XLA) Bruton agammaglobulinemia.	X-linked	Mutation at tyrosine kinase Btk
DiGeorge syndrome	AD	22q11.2 deletion
Severe combined immunodeficiency (SCID)	X-linked (m.c) and AR	
Chronic granulomatous disease (CGD)	X-linked and AR	
Hereditary angioedema	AD	deficiency of C1-esterase inhibitor

Genetic & Metabolic Disorders

Disease or syndrome	Mode of inheritance	Other
Epidermolysis bullosa simplex	AD	
Junctional epidermolysis bullosa	AR	
Dystrophic epidermolysis bullosa	AR or AD	
Niemann–Pick disease	AR	

Alkaptonuria	AR	
Ehlers–Danlos syndromes		specific gene affected determines the specific EDS
Marfan syndrome	AD	fibrillin gene (FBN1).
bilateral congenital cataract:	AD (50%)	
Abetalipoproteinemia (Bassen-Kornzweig syndrome)	AR	
Tuberous sclerosis complex	AD	
Incontinentia pigmenti	X-linked.	
Mucopolysaccharidosis except hunter syndrome (mucopolysaccharidosis II)	AR	
hunter syndrome (mucopolysaccharidosis II)	X-linked recessive	
maple syrup urine disease	AR	
Tyrosinemia type II	AR	
Isolated polydactyly	AD	
Fragile X syndrome	X-linked dominant	

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