Diphtheria -

is an acute infectious disease caused by ***Corynebacterium diphtheria*** and characterized by the appearance of a fibrinous membrane on the site of pathogen invasion (pharynx, larynx, nose, any others mucous membrane, skin wound) leading to symptoms of toxemia and toxic lesions of the cardiovascular system, nervous system and kidneys.

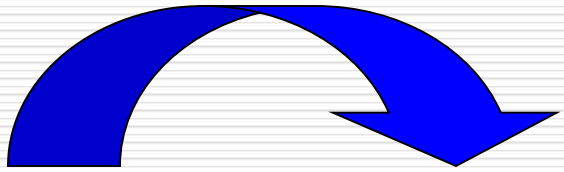
Etiology - *Corynebacterium diphtheria*

Is the only major human pathogen.

- Aerobe gram-positive bacillus
- Toxigenic and non-toxigenic
- The types of *C.diphtheriae:*
  - ✓ ***gravis,***
  - ✓ ***mitis,***
  - ✓ ***intermedius,***
  - ✓ ***belfanti.***
- Non-invasive, and most morbidity and mortality is associated with complications resulting from toxin elaboration.
- It successfully survives drying, low temperature and can stay on things, touched by the patient, not losing its pathogenic qualities for a long time.
- It is sensible: ultraviolet rays, high temperature, disinfectant agents, antibiotics (penicillin, erythromycin, cephalosporin)

Epidemiology

- The **source of the infection** is a human only:
  - ✓ **sick person**
  - ✓ **carrier**
- The patient becomes infectious from the **last day** of the incubation period.
- The highest epidemiological danger is presented by diphtheria **carriers** with chronic inflammatory disease of the upper respiratory tract (chronic adenoiditis, tonsillitis, bronchitis) who excrete the pathogen for a long time. High level of antitoxic immunity is not an obstacle against carriage of C.diphtheriae.



- **Seasonality**: during the cold months of the year.
- The mode of transmission:
  - ***Direct: air-droplet way***
  - ***Indirect: through contaminated objects, food***
- Susceptibility to diphtheria is determined by the presence of antitoxic immunity.
- Contagious index is 10-15 %.

Portal of infection

- mucous membranes of oropharynx,
- larynx,
- nasal cavity,

rarely:

- eyes,
- genital organs,
- damaged skin, burned or wound surface, intertrigoes, umbilical wound

Pathogenesis

- **Local:**
  - **Inflammatory lesion**
  - **Epithelium necrosis**
  - **Oedema**
  - **Fibrinogenous exudates**
  - **Pseudo-membrane**

Pathogenesis

At entry the bacilli multiply locally in the throat and elaborate a powerful exotoxin witch produce local and systemic symptoms.

Locally, toxin induces tissue necrosis, leukocyte response and formation of a tough, adherent pseudo-membrane composed of a mixture of fibrin, dead cells and bacteria-commonly over the tonsils, pharynx, or larynx. Any attempt to remove the pseudo-membrane results in bleeding.

The diphtheria bacilli within the membrane continue to produce toxin actively. This is absorbed and leads to distant parenchymatous degeneration, fatty infiltration and necrosis in heart muscle, kidneys tubular necrosis. The toxin also produces nerve damage (neuronal demyelination), resulting often in paralysis of the soft palate, eye muscles or extremities.

False membrane:

- **consistent and adherent !!!**
- Have 3 layers:

1. **Superficial – necrotic cels and different germs**
2. **Medium – fibrin**
3. **Profound – cellular detritus, leucocytes, C.diphtheriae**

Diphtheria bacilli don’t enter the blood!

They multiply at the level of portal of infection and secrete the exotoxin.

Morphopathology

Toxic myocarditis:

- Edema
- Cellular infiltration
- Degenerative lesion of myocardial febers
- Degenerative lesion of conductive system

Toxic neuritis:

- Degenerative modification in neurons and nerve fibers
- Paresis and peripheral paralysis

Toxic nephrosis - tubule lesions

Other organs - degenerative changes

Local - false membrane

Clinical manifestations of oropharyngeal diphtheria

Duration of the incubation period is from **2** till **10** days.

- There are **clinical forms**:
  - **localized:** ***catarrhal, patch (insular), film***
  - **wide-spread** (diffuse),
  - **subtoxic form**,
  - **toxic forms** (degree I, II, III)
  - **hypertoxic form**

Such classification is relative because there is complete correspondence between the local lesions and severity of toxemia.

The localized form of oropharyngeal diphtheria - local inflammation process, **encompassing the area of tonsils.**

- mild or moderate toxemia
- indisposition,
- anorexia,
- subfebrile body temperature,
- moderately sore throat,
- regional lymph nodes are moderately enlarged and painful.

The localized form of tonsillar oropharyngeal diphtheria

Forms:

- **Film (typical)**
- **Patch *(insular)***
- **Catarrhal (atypical)**

Carriage of the diphtheritic bacillus characterized by absence of any clinical manifestations.

The film form

- Is characterized by the appearance of continious fibrinous membranes in the form of a film, located on the tonsils.
- The fever reaches 38-39°C.
- Symptoms of intoxication are expressed moderately.
- Congestive hyperemia of the mucous membrane of the oropharynx.
- Moderate sore throat.
- Regional lymph nodes are enlarged and moderate painful.
- Sometimes clinical manifestations of cardiovascular disorders (appear tachycardia, dull heart sounds, systolic murmur).
- Duration of this clinical form is **6-7 days**: body temperature decreases in **2-3 days**, the patches remain for **6-7 days**.

The patch form

Takes place in the vaccinated children.

- It is characterized by typical fibrinous membranes in the form of grayish-white points (small islands) located out of the lacunae. The patches may be taken off without difficulty and bleeding of the mucous membrane may be present.
- The body temperature increases to subfebrile.
- Symptoms of intoxication are absent.
- The throat has no severe symptoms.
- Congestive hyperemia of oropharyngeal mucous membrane.
- Regional lymph nodes are moderately enlarged and painful.
- Timely bacteriologic tests have great significance in the diagnosis of diphtheritic infection.
- The complications are rare in this form of disease (mild forms of myocarditis).

The catarrhal (atypical) form

- Is registered in the foci of diphtheria.
- Symptoms of intoxication are absent or moderate.
- The body temperature is normal or subfebrile.
- Moderate congestive hyperemia of oropharyngeal mucous membrane.
- Reaction of the regional lymph nodes is not expressive.
- The diagnosis is confirmed by test results which show C.diphtheriae.

The widespread form of oropharyngeal diphtheria

- Is characterized by spreading of fibrinous membranes beyond the borders of the tonsils, on to the soft palate, lateral and back walls of the oropharynx, the palatal arches, the uvula.
- Regional lymph nodes are enlarged and painful.
- The body temperature increases up to 39°C, and higher.
- Headache, weakness, sore throat.
- Cardiovascular disorders are present since the onset.

The toxic (severe) form

- The onset is acute.
- The body temperature is 40°C or higher, severe headache, vomiting, anorexia, pallor, increasing weakness.
- The mucous membranes are edematous, with a cyanotic hue.
- The tonsils are enlarged, their surface is covered with thick whitish-grey, dirty-grey, or grey membranes with a rough surface. The membranes may be thin and taken off easily at the first hours of the disease. But they appear on the site again.

- The membranes **spread to uvula, soft and hard palate, the back wall of the pharynx**.

- There is severe edema of the mucous membrane of the oropharynx and adipose tissue of the neck. Depending on the spreading of edema three forms of toxic diphtheria are distinguished:
- **1st degree** - to the middle of the neck;
- **II-rd degree -** to the clavicles;
- **III-rd** degree - below the clavicles.

Hypertoxic form

- characterized by an abrupt onset and rapid development.
- Increasing toxemia is manifested by fever, severe prostration, mental confusion, convulsions since the first hours of the disease.
- The course is fulminant.
- Symptoms of intoxication predominate in the clinical manifestations of the disease and they leave behind the appearance of the membranes, edema of mucous membranes of oropharynx and adipose tissue of the neck.
- ITS is manifested by striking pallor, acrocyanosis, a drop of temperature of the skin and its "marmoreal" look, rapid thready pulse, dull heart sounds, decrease of blood pressure, oliguria.
- Lethal outcome will usually come on the 2nd-3rd day after the onset from progressive cardiovascular failure.

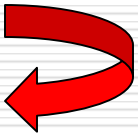
Nasal diphtheria - is more often observed in babies and may be found even in infants.

- In the majority of cases this form combines with oropharyngeal diphtheria.
- Difficulty of nasal breath, sanioserous nasal discharge with normal or subfebrile body temperature and satisfactory common condition occur. Then the discharge becomes mucopurulent and sanguinopurulent. Excoriations appear on to the skin at the entrance into the nose or on to the upper lip. Narrow nasal passages are determined by rhinoscopy.
- Depending on the nature of the lesions two forms are distinguished:
  1) **catarrhal ulcerous form - if erosions, ulcers or sanguinolent patches take place**
  2) **localized film form - if fibrinous membranes occur on the mucous membranes of the nose.**
- They are typical unilateral lesions, but if specific treatment is absent for a long time, the pathologic process may become bilateral or spread on the mucous membrane of the pharynx, larynx or on the skin.

The diphtheritic croup

I. **Croup cough period** begins gradually and its duration is usually from 1 to 3 days (in **1**-year-old babies — several hours). Fever is not high (up to 38°C). Malaise, anorexia, dry cough, hoarseness take place. Subsequently cough becomes paroxysmal, rough, and barking. The voice loses its sonority.

II. **Stenotic period** is characterized by aphonia and appearance of stenotic breath. Cough becomes soundless, refraction of complaisant places of the thorax appears. At first dyspnea manifests it self in children's restlessness or agitation (compensated stenosis) and later in the state of relaxation (subcompensated stenosis). Hypoxia is manifested by perioral cyanosis and tachycardia. In laryngoscopy grey fibrinous membranes are detected against the background of hyperemic mucous membrane of larynx and on the vocal ligaments.



In decompensated stenosis acute motor anxiety of the baby accompanies other symptoms. The baby jumps up, wants to be in the arms, tosses in bed. Cyanosis of the lips and the nasolabial triangle, cold sweat is registered. The pulse weakens or falls altogether when breathing in (paradoxical pulse). This is connected with the developing negative pressure in the thorax when breathing in. If in this period medical help (e.g. intubation or tracheostomy) is not rendered, asphyxia period will follow.

- **III. <u>In asphyxia period</u>** breath becomes arrhythmic and superficial. The baby becomes sleepy. Skin becomes grey and cold to the touch. Acrocyanosis appears. Reaction to painful stimulants is absent, reaction of pupils to light disappears. Tachycardia gradually becomes bradycardia and cardiac arrest follows.

Cutaneous diphtheria

- often appears as a secondary infection of a previous wound (pustule, ulcer and edematous rolled borders that may evolve as a chronic non-healing ulcer).

Diagnosis

The diagnosis is based on clinical manifestations:

- Fibrinous membranes of whitish-grey color are on the tonsils and spreading beyond them.
- Membranes are taken off with difficulty, leaving the mucous membrane bleeding.
- Congestive hyperemia and edema of mucous membrane of oropharynx, and edema of adipose tissue of the neck.
- Laryngoscopy may be used in the diagnostics of croup.

Laboratory tests include:

- Culture for C.diphtheria from the oropharynx, nose or the other suspected lesions
- Determination of antitoxic antibodies titer (protective titer is 1:40 and higher).
- PCR for C.diphtheria

- **Negative bacteriological tests do not exclude the diagnosis of diphtheria if typical clinical manifestations are present.**

Complications

- Myocarditis
- Nephrosonephritis
- Palatal, oculomotor paralysis
- Peripheral polyneuritis
- Pneumonia

Differential diagnosis

- Diphtheritic croup
- Stenosing laryngotracheitis (virus and bacteria)
- Infectious mononucleosis
- Measles croup
- Foreign body
- Papillomatosis of larynx

Antitoxic therapy

- Antitoxic therapy must be given promptly and in adequate dosage. Any delay increases the possibility that myocarditis, neuritis or death may occur. During an infection, diphtheria toxin may be present in three forms:
- non-bound;
- bound to the cells;
- internalized in cytoplasm.

Antitoxin will neutralize circulating toxin and may affect bound toxin. Because bacteriologic conformation of diagnosis cannot be obtained immediately, the decision to administer diphtheria antitoxin must be made on clinical and epidemiologic grounds.

Antibacterial therapy

- Penicillin, ampicillin, erythromycin, cephalosporin.
- In severe forms of the disease antibiotics should be given parenterally: penicillin, ampicillin, cephalosporins in a daily dosage of **50-100 mg/kg.**
- The treatment course must last till the liquidation of local process, but its duration must not be over **10-14 days.**
- **Antibacterial therapy is not a substitute for antitoxin treatment.**
- Eradication of the organism should be documented by culture.
- Persons who continue to harbor the organism after treatment, should take a recurrent course of therapy of another antibiotic during 7 days and follow-up cultures should be obtained.
- Diphtheria carriers should be treated using a similar scheme.
- **Booster dose of the diphtheria vaccine.**

Vaccines

- Universal immunization is the only effective control measure! (DTaP, Td)

Vaccination schedule în RM pentru anii 2016-2020

Vîrsta efectuării vaccinării	Imunizarea împotriva									Note
	Hepati-tei virale B **HepB**	Tuber-culozei **BCG**	Polio-mielitei **VPO**	Infecţiei cu rotavirus **RV**	Infecţiei Hib **Hib**	Infecţiei cu Pneumo-coci **PC**	Difteriei, Tetanosului, tusei convulsive **DTP**	Difteriei, Tetanosului **DT/Td**	Rujeolei, oreionului, rubeolei **ROR**	
24 ore	HepB-0*									În matern.
2-5 zile		BCG								În matern.
2 luni	HepB-1		VPO-1	**RV-1**	Hib-1	**PC-1**	DTP-1			Concomitent în aceeaşi zi: injectabil intramuscular HepB+DTP+Hib în componenţa vaccinului pentavalent, PC şi VPI separat cu diferite seringi şi în diferite locuri anatomice; VPO şi RV picături în gură
4 luni	HepB-2		VPO-2	**RV-2**	Hib-2	**PC-2**	DTP-2			
6 luni	HepB-3		VPO-3 VPI		Hib-3		DTP-3			
12 luni						**PC-3**			ROR-1	Separat cu diferite seringi şi în diferite locuri anatomice
22-24 luni			VPO-4				DTP-4			Concomitent, peste 16-18 luni după vaccinare
6-7 ani			VPO-5					DT	ROR-2	VPO-5 şi DT – concomitent primăvara, pînă la admiterea copiilor la şcoală; ROR-2 toamna (în clasa I)
15 -16 ani								Td	**ROR-3****	Concomitent (clasa 9), separat cu diferite seringi şi în diferite locuri anatomice
Adulţii: La 20, 30, 40, 50 şi 60 ani								Td		Imunizarea este efectuată la atingerea vârstei indicate

Notă:
1.Vaccinările **opţionale** recomandate în mod individual, inclusiv contra plată: contra Papilomavirusului uman – fetele de la vârsta de 12 ani 2 doze cu interval de 6 luni între ele; gripei – de la vârsta de 6 luni anual; hepatitei virale A - de la vârsta de 1 an 1 doză persoanele nevaccinate; infecţiei meningococice – vaccinuri mono- sau polivalente ne conjugate – de la vârsta de 2 ani, conjugate – de la vârsta de 2 luni; varicelei – de la vârsta de 9 luni pentru persoane care n-au suportat infecţia; tusei convulsive cu component pertusis acelular – membrii familiilor şi îngrijitorilor bebeluşilor.
2. Vaccinarea împotriva altor boli infecţioase (holera, tularemia, febra tifoidă, bruceloza etc.) va fi efectuată grupelor de populaţie cu risc sporit de infectare, în funcţie de situaţia epidemiologică şi în conformitate cu deciziile Ministerului Sănătăţii.
3. Imunizarea împotriva febrei galbene, encefalitei acariene, pestei va fi aplicată persoanelor care pleacă în regiunile endemice în mod individual, inclusiv contra plată.