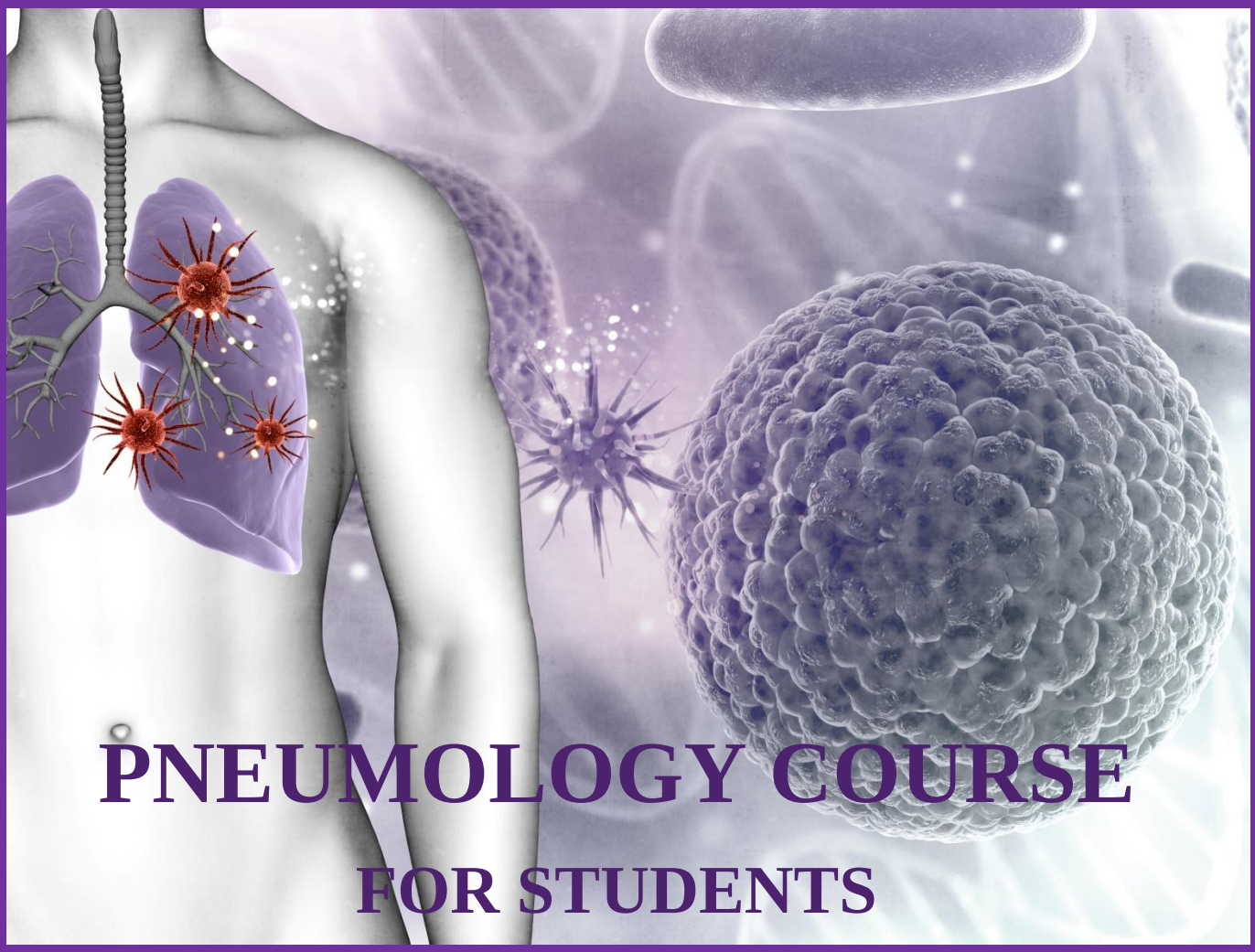
UMFT
Universitatea de Medicină și Farmacie „Victor Babeș” din Timișoara

PNEUMOLOGY DEPARTMENT



PNEUMOLOGY COURSE

FOR STUDENTS

Timișoara 2019

Authors (in alphabetical order):

- Bălă Gabriel, MD, PhD student, pneumology resident doctor
- Bertici Nicoleta, MD, PhD, Senior Lecturer
- Ciucă Ioana, MD, PhD, Senior Lecturer
- Crișan Alexandru, MD, PhD, Associate Professor
- Fira-Mlădinescu Ovidiu, MD, PhD, Associate Professor
- Frenț Ștefan, MD, PhD, Assistant Professor
- Hogea Patricia, MD, PhD student, pneumology resident doctor
- Manolescu Diana, MD, PhD, Associate Assistant Professor
- Marc Monica, MD, PhD, Associate Assistant Professor
- Mihăicuță Ștefan, MD, PhD, Senior Lecturer
- Mihuța Camil, pneumology resident doctor
- Oancea Cristian, MD, PhD, Professor
- Pescaru Camelia, MD, PhD, Assistant Professor
- Pop Liviu-Laurențiu, MD, PhD, Professor
- Porojan-Suppini Noemi, MD, PhD student, Associate Assistant Professor
- Socaci Adriana, MD, Phd, Tuberculosis Department Coordiantor
- Țiplea Cosmin, MD, specialist pneumology doctor
- Trăilă Daniel, MD, PhD, Assistant Professor
- Tudorache Emanuela, MD, PhD, Associate Assistant Professor
- Tudorache Voicu, MD, PhD, Professor

Editura „Victor Babeș"
Piața Eftimie Murgu 2, cam 316, 300041 Timișoara
Tel./Fax: 0256495210
e-mail:evb@umft.ro
www.umft.ro/editura

Director general: Prof. univ. emerit dr. Dan V. Poenaru
Director: Prof. univ. dr. Andrei Motoc

Colecția: MANUALE
Coordonator colecție: Prof.univ.dr. Sorin Eugen Boia

ISBN 978-606-786-157-0

CONTENT

1. ANAMNESIS AND PHYSICAL EXAMINATION OF THE PATIENT WITH RESPIRATORY PATHOLOGY. ELEMENTS OF FUNCTIONAL ANATOMY

”EVERY MAN is
… Like all other men,
… Like some other men,
… Like no other man”
(Kluckhohn C, Murray HA., Personality in Nature, Society and Culture., 1948)

I. Anamnesis and physical examination of the patient with respiratory pathology

A careful and complete medical history completed with a thorough clinical examination, are the strengths of a good clinician. For a correct diagnosis, it is important to continue collecting anamnestic information as they become available.
1. Major pulmonary symptoms:

Dyspnea is described by the patient as "shortness of breath", "choking sensation", "inability to draw air in the chest", "fatigue"; According to ATS (American Thoracic Society) dyspnea is a subjective perception of respiratory distress, variable in intensity, consisting of qualitatively distinct sensations.

- The Borg Scale, and questionnaires, such as the mMRC (Modified Medical Research Council) Dyspnea Scale (Table 1) and Pulmonary Functional Status and Dyspnea Questionnaire can be evaluated.

Table 1. mMRC (Modified Medical Research Council) Dyspnea Scale

0	Dyspnea from intense physical effort
1	Dyspnea from sustained walking or on easy slope
2	Dyspnea prevents walking at the same pace with an individual of the same age or requires stops on a flat ground
3	Important dyspnea that requires stops after 100m or a few minutes of walking on flat ground
4	Severe dyspnea in daily activities (getting dressed)

It can be determined by cardiac, pulmonary, neuromuscular, metabolic, hematological pathologies. Figure 1 shows the dyspnea diagnosis algorithm

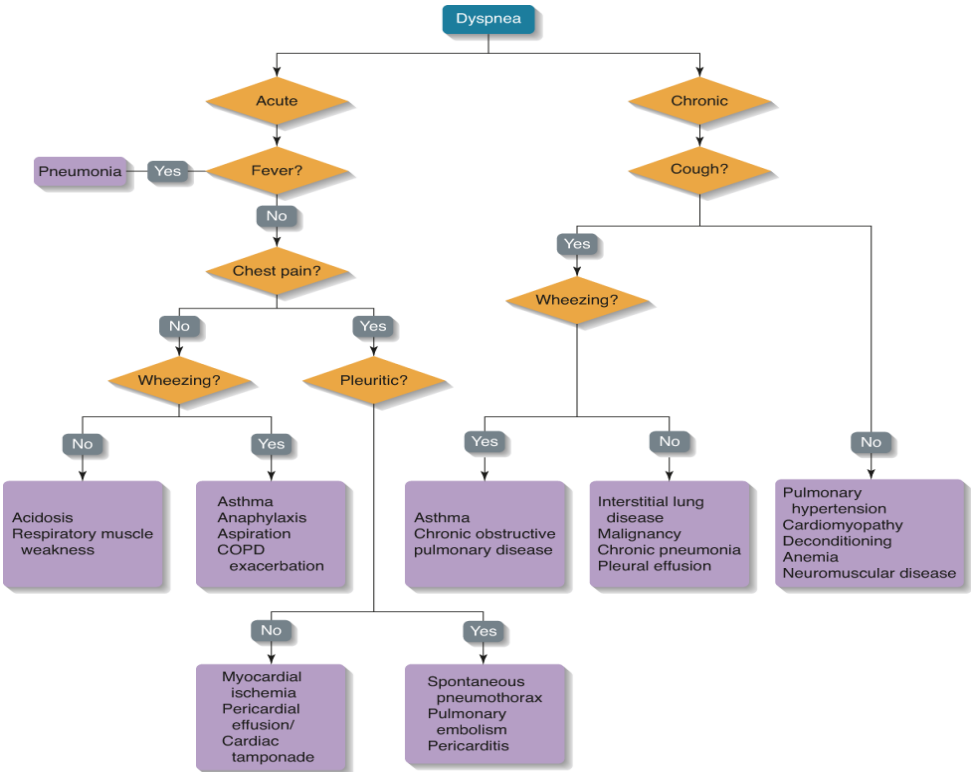


Figure 1. The diagnostic algorithm for dyspnea

Cough is an essential reflex mechanism (abrupt expiration with closed glottis), with the protective role of the airways from harmful substances, and the protective role of the lungs by draining excess secretions.

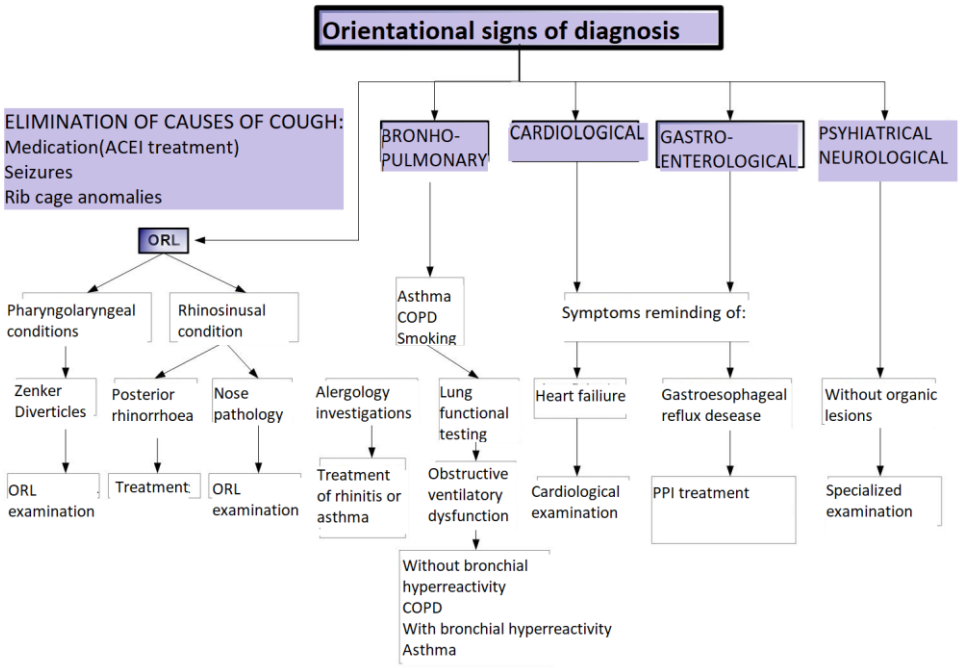


Figure 2. Cough diagnosis algorithm

In the evaluation of a coughing patient, special attention is paid to the following aspects: whether the onset is acute or chronic, whether it is productive or not, the type and quantity of sputum, associated symptoms.

Hemoptysis - the elimination by cough of an amount of blood. When it appears de novo, it requires a thorough examination, including tomographic examination, bronchoscopy.

The quantity can be: small (under 50 ml), medium (50-100 ml), large (100-300 ml), massive (over 300 ml).

Differential diagnosis: haematemesis (digestive pathology, preceded by nausea, colored black- in coffee grounds, accompanied by alimentary content), posterior epistaxis (preceded by salty taste, eliminated by mouth without effort of vomit, highlighted by the objective examination on the posterior pharyngeal wall).

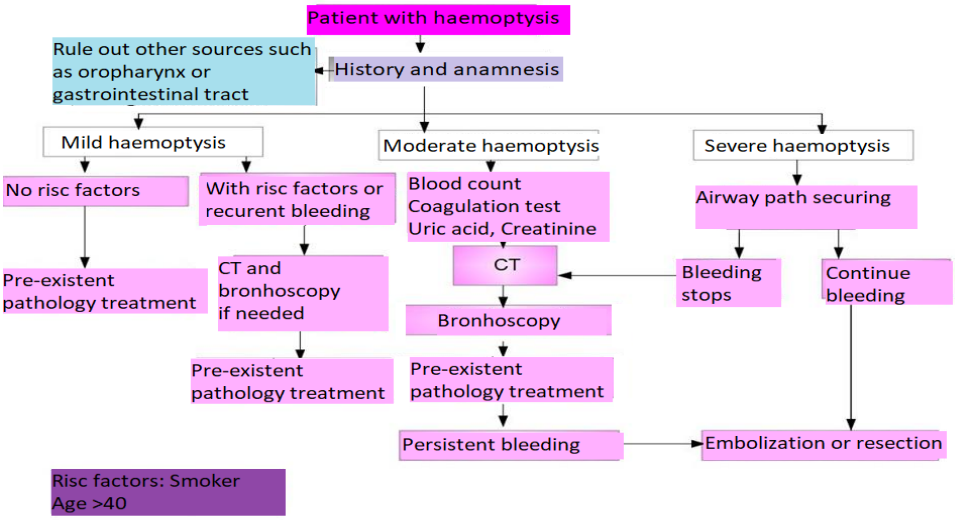


Figure 3. Algorithm for diagnosis of patients with hemoptysis

Chest pain

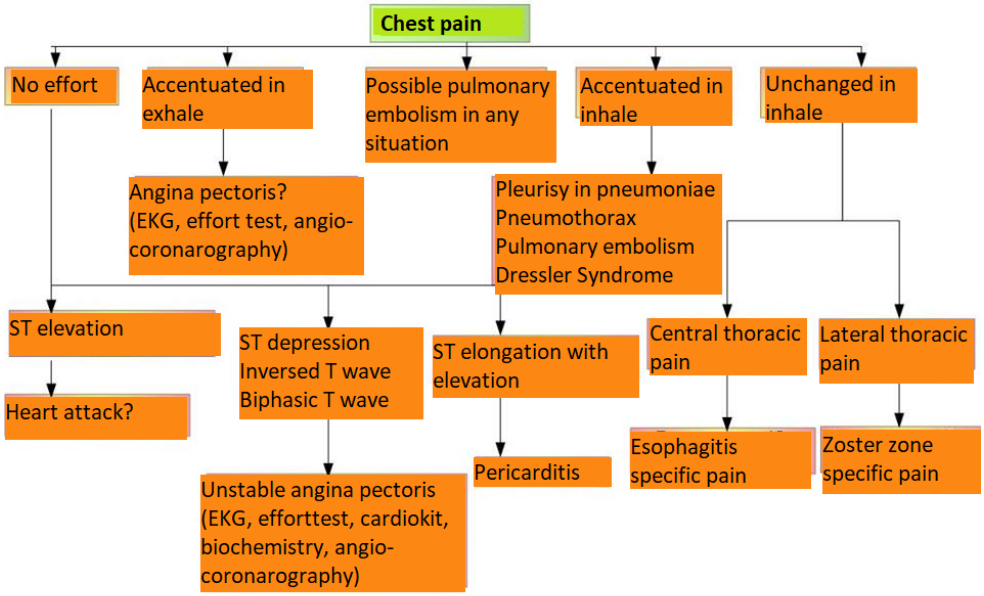


Figure 4. Diagnostic algorithm of the patient with chest pain

2 Family history: provides information on genetic diseases, such as cystic fibrosis, alpha 1-antitrypsin deficiency, Rendu-Osler's disease, imotile cilia syndrome, etc. Family exposure to contagious diseases such as tuberculosis can be identified.

3. History of smoking, other pollutants: the patient should be asked about the smoking habit, if he has ever smoked. If the answer is positive, you should ask when he started smoking, when he stopped smoking, how much he smoked, respectively about different forms of tobacco and exposure in the workplace or at home. In developing countries, steaming, smoke from cooking inside, wood burning stove can be a major risk factor for lung diseases, especially among women.

4. Medication and Allergies: To be noted the complete medication of the patient, possible allergic or toxic reactions that occurred to these drugs. Consumption of alcoholic beverages (their type and quantity) should also be asked and noted.

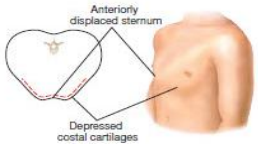
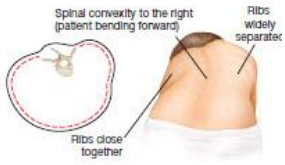
5. Occupational history: Identifying the relevant occupational exposure can lead to job change, thus preventing progressive and irreversible pulmonary destruction.

6 Travel history: Previous homes in endemic areas for fungal infections such as histoplasmosis or coccidioidomycosis may be helpful in diagnosis. A recent travel history may bring the disscussion of the possibility of contacting diseases specific to certain geographical areas.

II. Objective examination of the chest

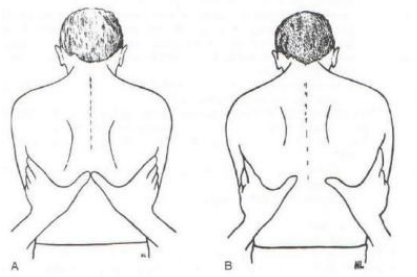
Inspection: of the skin and soft tissue: scars, color changes, edema, tumor formation can be identified

Table 2. Chest deformities

Barrel chest - globular appearance (antero-posterior diameter = 1), obtuse xiphoid angle, raised shoulders, short neck, full subclavicular pits, horizontal ribs, wide intercostal spaces; met in COPD, BA.	
Chest with sunken sternum (pectus excavatum) - sunken sternum in cone shape, the heart is rotated and pushed laterally.	
Chicken chest (pectus carinatum) – sternum is shifted anteriorly, antero-posterior diameter isenlarged.	
Thoracic kyphoscoliosis - abnormal curvature of the spine, rotation of the vertebrae.	

Palpation: it is necessary for the examination of the breasts, lymph nodes, bone deformities (such as cervical rib, subcutaneous calcinosis, multiple sclerosis)

- palpation of respiratory enlargement



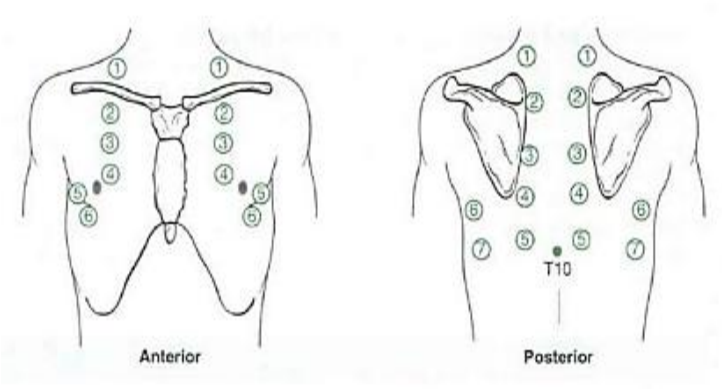
The patient positioned in orthostatism, the doctor is behind the patient, with the palms located on his chest wall, forming two skin folds between the patient's spine and the two police officers. At the time of inhale, the doctor's hands are drifted apart, the skin folds disappear, and in exhale they return to their original position

Figure 5. Palpation of respiratory enlargements: A. Exhale; B. Inhale (According to Illustrated Guide for Respiratory System Examination, Dr. Farid Ghalli, 2016)

When respiratory enlargements are diminished, the folds remain present even in inhale (apical: tuberculosis, neoplasm, pahipleuritis; basal: pleurisy, pneumothorax, pahipleuritis, pneumonia, neuralgia).

- Palpation of the quiver of the chest: the patient positioned in orthostatic or sitting position, the doctor is behind the patient, with palms symmetrically palpating his chest wall while the patient will repeatedly say 33 (thirtythree). The quiver can be altered in bronchial obstructions, pulmonary emphysema, thick chest wall, pleurisy, pneumothorax.

- **percussion**



This technique evaluates the loudness of the pulmonary parenchyma, by creating vibrations in the tissues. Maneuver: the doctor's left hand is applied to the patient's chest, with his fingers separated, the medius is placed in the intercostal space, parallel to the ribs, and with the medius of the right hand bent, the middle phalange of the left medius is percutted.

Figure 6. The sites of percussion and pulmonary auscultation (According to Illustrated Guide for Respiratory System Examination, Dr. Farid Ghalli, 2016)

Table 3. Percussion of the chest

Hipersonority	Diffuse	Thin chest wall, Pulmonary emphysema Pneumothorax
	Located	Caverns, Evacuated cysts, Evacuated abscesses
dullness	Fluid	Pahipleuritis, Plural effusions
	Lung condensation with free bronchitis	Pneumonia, Lung Infarction, Stasis
	Atelectasis	

- **Auscultation:** appreciation of the passage of air flow through the tracheobronchial tree and the parenchyma pulmonary; Maneuver **:** The patient breathes deeply, mouth open.

Breathing types	Characteristics	Causes
Apnea	Prolonged breathing pauses	Cardiac arrest
Biot breathing	Irregular breathing with long apnea periods	Intracranial hypertension
Cheyne-Stokes breathing	Irregular type of breathing; breath grows and decreases in depth and frequency alternating with apnea periods	Central nervous system diseases; Congestive heart failure
Kussmaul breathing	Deep and rapid breathing	Metabolic acidosis
Staccato breathing	Prolonged inhale	Cerebral injury
Paradoxal breathing	Partial or global movement towards interior of the ribcage in inhale, and towards exterior in exhale	Chest trauma; Dyphragm paralysis; Muscular fatigue
Asthmatic breathing	Prolonged exhale	Airway obstruction

Physiological respiratory noises: physiological tubular blowing, broncho-vesicular respiration, vesicular murmur (MV).
A. Modification of vesicular murmur:
- Tight breathing: bronchiolitis, tachypnea
- Decreased MV: obstructive causes (high: foreign bodies, glotic edema associated with stridor, low: COPD, asthma crisis, endobronchial tumors associated with wheezing); restrictive causes: pneumonia, diffuse interstitial pneumopathy, changes in the chest wall (kyphoscoliosis), small pleurisy, pneumothorax
- MV abolition: severe asthma attack with bronchoplegia, atelectasis, massive pleurisy, massive pneumothorax, massive pahipleuritis
B. Adventitious Breath sounds

Table 4. Pathological respiratory noises

Rales				**Friction rub**
Bronchial rales *-in both times of the breath* *- modified by cough*		**Bronchovascular rales** - by bubbling the fluid from the alveoli / bronchioles / cavities		- by rubbing the two thickened pleural sheets on which fibrin was deposited - does not change after coughing In: pahipleuritis, after evacuation of pleural fluid, carcinomatous infiltration
Wheeze *-high-pitched*	**Rhonchus** - snoring character	**Crackles** - at the end of the inspiration	**Subcrackles** - at the beginning of the inspiration, in exhale	
Bronchial asthma *COPD*	Bronchitis Bronchiectasis Pulmonary neoplasm Foreign bodies	Pneumonia Pulmonary infarction Diffuse interstitial pneumopathies	Bronchopneumonia Pulmonary stasis Bronchitis Bonchiectasis	

Depending on the time of appearance, inspirational rales can be characterized as follows:

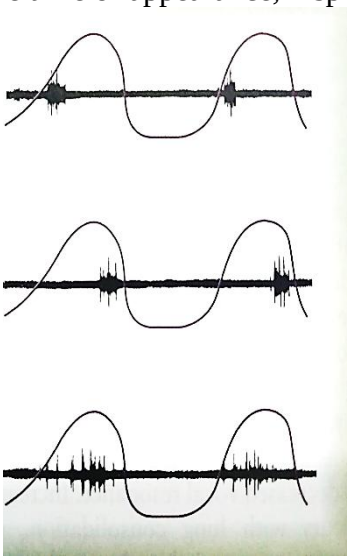


Figure 7. Inhale rales
(*adapted after *Egan's fundamentals of respiratory care, 8th ed.)

2. Elements of functional anatomy of the patient with respiratory pathology

The respiratory system consists of all the organs that contribute to the exchange of gases between the body and the external environment, ensuring their homeostasis. Table 1 shows the main functions of the respiratory system.

Table 5. Functions of the respiratory system

Function	**Effector**
Breathing control	Respiratory centers, peripheral chemoreceptors, afferent and efferent nerves
Ventilation pump	Chest wall, pleura, respiratory musculature
Distribution of ventilation	Upper and inner airways, bronchioles
Blood distribution	Pulmonary arteries and veins, capillaries
The gas exchange	Terminal respiratory unit
Clearance and defense mechanisms	Mucociliary escalator, alveolar clearance, pulmonary lymphatics

1. Breathing control

The innervation of the lung is provided by the vegetative nervous system (the medullary center) through the anterior pulmonary nerve plexus and the posterior pulmonary nerve plexus.
The motor innervation represented by the sympathetic nervous system, more precisely by the postganglionic fibers, which provides the bronchodilating, vasodilating action, the relaxation of the bronchial muscles. Regarding the parasymaptic activity (performed by the Vagus nerve), it causes bronchoconstriction, vasoconstriction, mucus hypersecretion.
In certain situations, voluntary respiratory control may exceed the respiratory centers at the brain stem level, the orders start at the cortical level. Such examples are apneea, hyperventilation,

cases in which blood gas alterations may occur. Other examples are: voluntary coughing, singing, talking, measuring maneuvers of vital capacity.
Thoracic wall mechanoreceptors*:* compounds from receptors in the muscle fibers and tendons, measure and modulate the forces generated by the inspiratory effort.
Pulmonary mechanoreceptors**:** there are 3 types: irritation (located in the epithelium, producing bronchoconstriction, tachypnea in contact with pollutants), stretching (at the level of smooth muscles, respond to changes in lung volume), juxtacapillary (at the level of the alveolar wall, stimulation edema, fibrosis).
Chemoreceptors **:** detects changes in the level of PaO_2, $PaCO_2$, pH, sends signals to the respiratory centers to correct ventilation in case of changes in the metabolic needs of the body.

Table 6. PaO2, PaCO2 pressures

	$PaCO_2$ (mmHg)	**PaO_2 (mmHg)**
Hypoventilation	80	40
Normal	**40**	**90**
Hyperventilation	20	115

The effects of PaCO2 modification - carbon dioxide is the most important chemical stimulus in the regulation of respiration (the ventilation per minute increases with CO_2 level). The chemoreceptors from the peripheral circulation and the CNS detect the differences and send signals to the associated respiratory centers, to correct the ventilation. The body's ability to store CO_2 exceeds its oxygen storage capacity, so changes in the dynamics of ventilation will occur faster and will be more significant in the case of changing the PaO_2 level.
The complete stop of the ventilation for 1 minute of a person (breathing in the air in the room), will cause the increase of 6-10 mmHg of $PaC0_2$ and the decrease of PaO_2 by 40-50 mmHg.

The effects of PaO_2 modification - hypoxia determine the increase of the ventilatory effort by stimulating the peripheral chemoreceptors at the carotid and aortic level, and at the central respiratory depression level.

Changing pH - both hydrogen ions (stimulates peripheral and central chemoreceptors) as well as changes in $PaCO_2$ level change ventilation. Increased ventilation per minute can also be determined by decreasing the pH to constant $PaCO_2$ values.

2. Ventilation pump
It is composed of the thoracic wall (spine, ribs, sternum, connected by ligaments and cartilages), respiratory musculature and pleural space.
The respiratory musculature is composed of the *inspiratory* muscles (diaphragm, inspiratory intercostal muscles, scalenes, sternocleidomastoids).

- Under normal conditions the expiration does not require active work of the musculature (internal intercostal muscles, abdominal wall musculature), but this may be necessary in pathological conditions such as obstructive diseases.
- The fatigue of the respiratory muscles is translated by the increase of the respiratory frequency, superficial breaths, tachypnea, the growth of PaCO2, later respiratory acidosis. In this situation, the accessory function of the accessory muscles creates negative pressure in the chest, with the diaphragm ascending, making the *paradoxal breathing.*

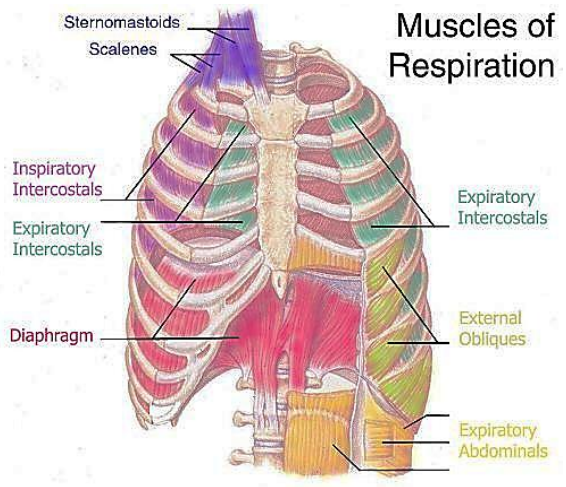


Figure 8. Respiratory muscles

Pleurae: is a serous membrane that forms the coating of the lung, it is composed of 2 parts: parietal pleurae (6 layers) - it contains numerous pain receptors, derived from the nerves of the intercostal musculature, their irritation produces the *pleuritic chest pain*; respectively visceral pleurae (5 layers). The pleural cavity is a virtual space, contains 1-15 ml of fluid, which plays a role in the mechanics of breathing.

3. Air distribution

The upper airways have a role in purifying, heating, and humidifying the air:

- Nasal cavity - is composed of nasal pits, separated by the nasal septum.
- Pharynx - has digestive and respiratory function
- Larynx - contains vocal cords, which play a role in coughing (by closing vocal cords and contracting the respiratory and abdominal muscles. It is a major clearance mechanism for material collected in large airways, initiated by nerve endings from the tracheae and large airways).

This segment of the airways is colonized with saprophytic germs, sometimes pathogenic germs, which, passing through the glottic barrier, are responsible for infections at this level.

Lower airways include trachea, main bronchi, terminal bronchioles, respiratory bronchioles.

Trachea - starts from the base of the neck, extending to the level of the fork of the main bronchi, called carina (length = 10-12cm). It is located anterior to the esophagus, and posterior to the aorta. It consists of 15-20 incomplete cartilaginous rings, posteriorly connected by fibrous bands.

The main bronchi - at the T4 level (the pulmonary spine) the trachea branches into the 2 main bronchi, which subsequently branch off, forming the bronchial tree. This structure is similar to the trachea, fibro-cartilaginous. The right bronchus is shorter (2.5 cm), thicker, with a more vertical path, favoring the appearance *of suction pneumonias* on this side. The left main bronchus is thinner and longer (5 cm), with a more horizontal path. Irritating receptors at this level may initiate cough reflex, and motor stimuli of the vagus nerve cause bronchoconstriction and mucus hypersecretion. The main bronchus wall is composed of 4 tunics (see table 7).

	Cells	
Mucous	Cilia-cylindrical, caliciform (mucus secretion), Dendritic, undifferentiated, neuroectodermal (secretion mediators and hormones)	May be affected by inhalation pollutants, infections, lowering the body's defense capacity Tumors, foreign bodies may occur
Lamina propia	Elastin, collagen, blood vessels, lymphatics, nerve fibers	
Submucosal	Glandular tissue	
Fibro-cartilaginous	Elastic fibers, collagen, cartilaginous ring	The absence of cartilaginous ring, structural alterations determines at this level traheobronhomalacy, changing the caliber and the trajectory of bronchi = bronchiectasis.

The bronchial tree is formed through the division of the main bronchi as follows: lobe- segmentation- supralobular- intralobular- terminal. The terminal bronchioles are less than 1 mm in diameter, consisting predominantly of smooth muscle tissue

Up to this level their main function is air management. They are then divided into respiratory bronchioles (acinar, lined by flat, paved epithelial cells, the ciliated cells disappear at this level), which are part of the intermediate zone, followed by the alveolar channels, alveolar sacs, respectively alveoli (300 mil. Alveoli). These form the respiratory surface, approx. 70sqm (the size of a tennis court).

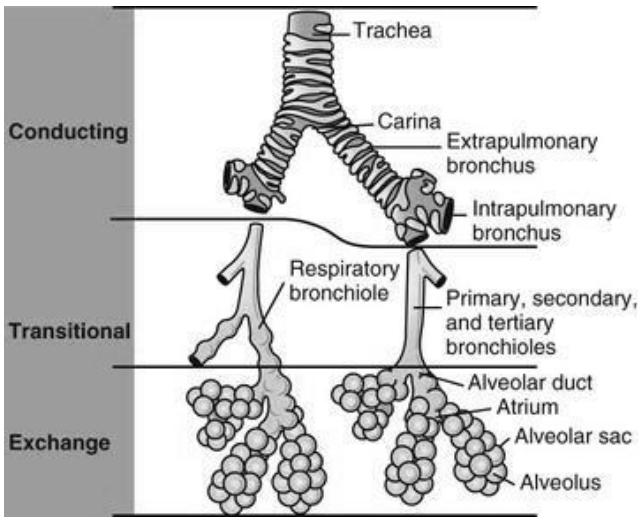
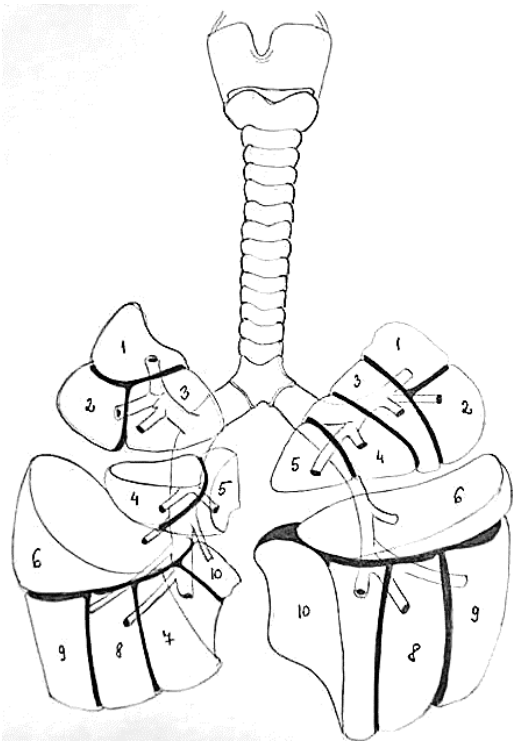


Figure 9. Pulmonary arborization

Pulmonary segment: it is the morphological and functional unit, it is composed of several lobules. It is anatomical territory with precise boundaries, the own bronchovascular pedicle.



Legend

Upper lobes (1) apical, (2) posterior, (3) anterior, (4) superior lingular, (5) inferior lingular; Middle lobe: (4) lateral, (5) medial; Lower lobes (6) apical (superior), (7) medial, basal, (8) anterior basal, (10) posterior basal. The medial basal segment (7) is absent from the left lung.

Figure 10. Pulmonary segmentation

4. Blood distribution

Pulmonary vascularization is double:

- Functional 100% of the cardiac output, realizes the gas exchanges (small circulation)

At a heart rate of 80 beats / minute, the gas exchange in 100ml of liquid from the pulmonary capillaries takes 0.75sec. In the case of physical effort, the blood flow increases, reducing the time required for gas exchange.

- Nutritious 2% of cardiac output, through arteries (derived from aorta) and bronchial veins (large circulation). These follow the path of the bronchial tree.

5. Gas exchange

Terminal respiratory unit (acini) = pulmonary portion distal to non-respiratory bronchiole

3-5 acini form the pulmonary lobe; they are separated from each other by septa visualized through the Kerley B lines in the case of fluid or fibrosis accumulations.

The terminal bronchiole enters the terminal respiratory unit, accompanied by the branching of the pulmonary artery, supplying non-oxygenated (venous) blood from the right ventricle. It is divided into a rich capillary network that covers the alveolar wall, and drains into the pulmonary venules located at the periphery of the alveolus.

Alveolar cells - 5 types:

Cellular type	*%*
Type 1 pneumocytes	8.3
Pneumocytes type 2	15.9
Endothelial cells	30.2
Interstitial cells	36.1
Macrophages	9.4

The number of endothelial cells is higher than the pneumocytes, which is why the effect of pollutants is more harmful to the cardiovascular system than to the respiratory system.

The alveolar epithelium and the capillary epithelium form the alveolo-capillary membrane, allowing the gas exchange through diffusion. The thickening of this membrane determines the decrease of the capacity of gas diffusion (interstitial pneumopathy, fibrosis). The surface of the alveolar epithelium is covered by a thin surfactant film. Alteration of it causes alveolar collapse (alveolar prosthesis, SDRA).

Interstitial cells - provide structure to the alveolar walls. Alveolar macrophage plays an important role in alveolar clearance. Type 1 pneumocytes cover the surface of one or more alveoli through cytoplasmic extensions. The destruction of type 1 pneumocytes causes the proliferation of type 2 pneumocytes. They have the ability to carry electrolytes, which plays a role in the resolution of edema.

6. Alveolar clearance and defense mechanisms

Passage of particles in the airways : particles with a diameter greater than 10 microns are deposited in the upper airways passage, those between 2-10 microns at the level of the bronchial tree, and those between 0.5-3 microns can penetrate the level of the terminal respiratory unit.

Pulmonary transport system : it has a role in the removal of the particles reached at the alveolar level, it is composed of:

- Mucociliary escalator: it is made up of ciliated epithelial cells, mucus producing cells. The mucus is the transport medium of the particles and is made up of 2 layers: gelatinous upper, which captures the particle, and a lower, more liquid layer, through which the microvilli of the cells can move easily. It transports the particles from the terminal bronchioles to the large airways, from where they can be eliminated by coughing, expectoration, or swallowing. The transport speed is 3mm / minute, and increases at the proximal level. 90% of the mucosal particles are removed in 2 hours.

Cigarette smoke or other harmful inhalers can "paralyze" the movement of the cilia, causing the mucus to stagnate, favoring the multiplication of microorganisms. A particular situation is the immobile cell syndrome.

- Alveolar macrophage - phagocytic cell of the alveolar wall; is a monocyte from the bone marrow, which can adapt to the oxygenated environment at the alveolar level. It plays a role in detoxification, destruction and transport of particles that have reached the alveoli. If the macrophage cannot phagocytose the particles (bacterial toxins, large quantities), it produces humoral factors that cause the migration of neutrophils and other phagocytic cells to the lung, as the second line of defense.

- Lymph-hematogenous drainage - the environment of migration of macrophages from the alveoli under inflammatory conditions. Migration through lymphatic vessels can take months, years. Collections of macrophages with foreign particles can be observed in the pulmonary lymph nodes, where they can remain throughout life.

References

1. Pneumology course for resident doctors, edited by Voicu Tudorache, Mirton Publishing House 2013, pages 7-15
2. Murray & Nadel's Textbook of Respiratory Medicine, 6th ed., 2016 Saunders, Elsevier, pp. 263- 277
3. Medical Semiology vol. 1, edited by Mirela Cleopatra tomescu, Victor Babes Publishing House 2010, pages 139-162
4. An Illustrated Guide to Respiratory System Examination, Dr. Farid Ghalli, 2016
5. OSCE And Clinical skills handbook: Hurley KF, second edition.Elsevier Canada 2011
6. OSCEs at a glance, first edition 2013
7. Macleod`s Clinical Examination, thirteenth ed. 2013
8. Step by Step Clinical examination Skills: Iqbal F, first edition 2009
9. ERS Handbook of Respiratory Medicine 2nd Edition, publisher European Respiratory Society, 2013
10. Harrison's Pulmonary and Critical Care medicine, 2nd edition, Joseph Loscalzo, 2013, pages 2-45
11. Chest medicine, Essentials of pulmonary and critical care medicine, second edition, Ronald B. George, Richard W. Light, Michael A. Matthay, Richard A. Matthay, 1990, pp. 3- 73
12. A guide to phisical examination and history taking, fifth edition, Barbara Bates, 1991, pp. 3-26
13. Egan's Fundamentals of Respiratory Care, Eighth Edition, Robert L. Wilkins, James K. Stoller, Craig L. Scanlan, 2003, ISBN 0-323-01813-0, pag 1-37
14. http://www.bimjonline.com/Imageoftheweek/Imagewk31%2805-09-2011%29.htm

2. FUNCTIONAL PULMONARY EXPLORATION IN CLINICAL PRACTICE

Introduction

Functional pulmonary testing allows accurate, reproducible evaluation of the functional status of the respiratory apparatus. Through the detected changes, these tests help quantify the seriousness, they facilitate early diagnosis and the evaluation of response to treatment for chronical pulmonary diseases.

The results one gets through functional testing are to be interpreted only in a clinical environment, as they have no specificity when it comes to the causes of the disease, but only affect the mechanisms that regulate lung function.

Some simple test can be carried aut with no difficulty even in a GP's office:

- pulsoximetry;
- spirometry.

Others, on the contrary, require costly equipment and qualified staff:

- body-plethysmography;
- measuring the gas transfer rate Dlco (gas diffusion test);
- analyzing blood gas (arterial blood gases);
- bronchial challenge tests;
- cardio-pulmonary effort testing (exercise stress test).

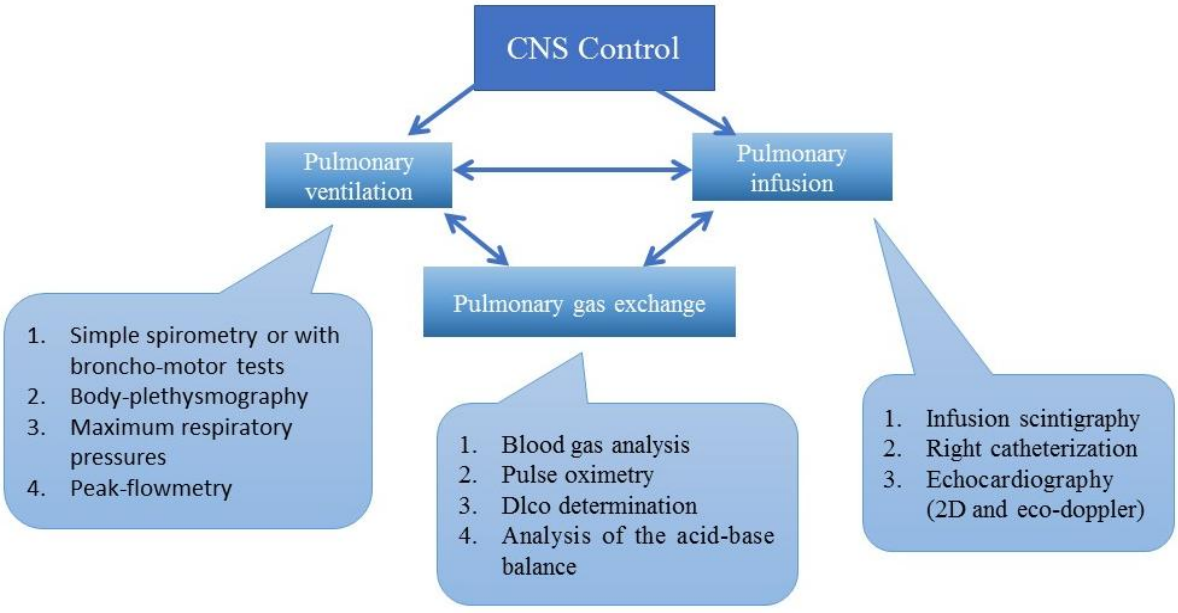


Figure 1. The main tests according to the analyzed mechanism ans symptoms (Adapted after Pneumology Course for resident doctors under the editorial Voicu Tudorache, Mirton 2013 edition)

I. Tests of pulmonary ventilation

Before testing pulmonary ventilation, it is important for the patient not to smoke for at least 1 hour previously, not to have any alcohol for at least 4 hours before, not to have stressful physical effort/heavy exercise for at least 30 minutes before and not to have had a heavy meal for at least 2 hours before. Patients should also avoid wearing tight clothing that might hinder chest and abdomen expansion.

A. Spirometry

This is a simple test, useful in the diagnosis and evaluation of chronical lung diseases. The test measures the amount of air inhaled and exhaled in a time unit (ventilation flow).

Table 1. Indications, contraindications and complications of spirometry

Indications	Contraindications	Complications
• Detecting presence/absence of ventilatory disfunctions • Assessing change of lung function over a period of time, disease preogression or response to treatment • Evaluating response to professional or environmental emissions • preoperatory, in order to asses the risk rate of surgical procedures that might affect lung function	• hemoptysis • pneumothorax • unstable cardiovascular disease • cerebral aneurysm • recent eye surgery • recent abdominal, otorhinolaryngologic or chest surgery • dementia	• pneumothorax, • intracranial hipertension • syncope, dizziness • chest pain • paroxysmal cough • worsening respiratory failure • bronchospasm • contamination with nosocomial germs

In order to get quality data, both the expirogramm and the flow-volume curve have to be recorded, and the criteria of acceptability and repeatability of respiratory maneuvers have to be met.

Table 2. Criteria of acceptability and repeatability of respiratory maneuvers in spirometry. *(Adapted from Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013)*

Criteria of acceptability:

1. Corresponding beginning of expiration, without hesitancy or false extrapolation (extrapolated volume smaller than 150ml or smaller than 5% of the forced vital capacity, depending on which value is bigger).
2. Full expiration (longer than 6 seconds and obtaining a plateau on the forced expirogramm).
3. No occurency of artefacts like:
   - cough in the first second of forced expiration or other episodes of cough that, according to the technicians judgement, interfere with the accuracy of the results;
   - effort that is not maximal during the whole period of expiration;
   - premature closure of the glottis;
   - early termination of the expiration;
   - obstruction or loss of air in the mouth.

Criteria of repeatability:

The first two maximum values of **FVC** (forced vital capacity), respectively of ale **MEVS** (maximum expiratory volume per second), do not differ more than 150ml (if FVC < 1l, the difference should not be more than 100ml).

The data on lung volume and forced flows obtained by spirometric measurement are compared to the predicted data, corresponding to the *age, height, sex and race* of the patient. When interpreting spirometry, we considerthe highest values of the forced vital capacity (FVC) and of the maximum expiratory volume per second (MEVS) obtained in at least 3 acceptable measurings, and for the rest of the ventilatory parameters we consider the values from the maneuver with the highest sum of FCV and MEVS. Though the most correct approach is the one comparing each parameter to the lower limit of its normal, we consider **normale** the percentual variations between **80-120% of the predicted value**. For expiration flows compared to FVC, too, we can use default values setting the boundaries of normality:

- **MEVS/FVC (indicator for bronchic permeability IBP) ≥ 0,7**;
- **FEF50%/CVF (indicator for distal permeability IDP) ≥ 0,8.**

Table number 3 presents respiratory disfunctions and the main spirometric parameters analysed. When speaking about obstructive disfunctione (for example bronchial asthma, chronic obstructive bronchopneumopathy, cystic fibrosis, bronchiectasis, foreign bodies, endobronchial tumors, post-tuberculous syndromes) in early stages, we can find modifications only for parameters of distal obstruction that is: **MEV25-75%**, respectively **FEF50%/FVC are low.**

Table 3. Ventilometric parameters in ventilatory disfunctions
(Adapted from Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013)

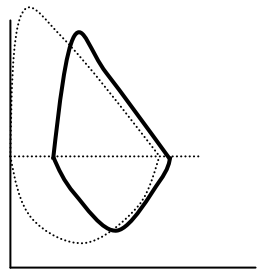
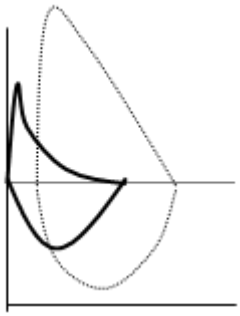
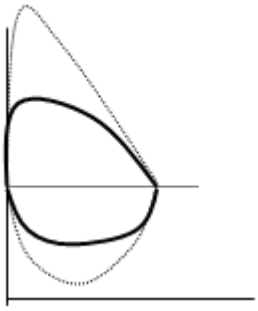
Parameter	**Distal obstructive syndrome**	**DV obstructive**	**DV restrictive**	**DV mixed****
CVF	N	N (possible ↓)	↓	↓
MEVS	N	↓	↓ (possible N)	↓
MEVS/CVF	N	↓	N (possible ↑*)	↓
$MEV_{25-75\%}$	↓	↓	↓ (possible N or ↑*)	↓
$FEF_{50\%}$ /CVF	↓	↓	N (possible ↑*)	↓

Severity of respiratory disfunction (in order to appreciate this severity, the consent about interpreting strategies for functional testing recommends the use of MEV, percentually expressed from the predicted value) can be:

- light MEVS > 70% prez.
- moderate MEVS = 60 - 70% prez.
- moderate-severe MEVS = 50 - 59% prez.
- severe MEVS = 35 - 49% prez.
- very severe MEVS < 35%

The aspect of the flow-volume curve can furnish data on the type of ventilatory disfunction (see table 4).

Table 4. The aspect of the flow-volume curve ***(Adapted from Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013)***

Restrictive syndrome	**Tipical obstructive syndrome** (asthma, BPOC)	**Obstructive syndrome of the upper respiratory tract** (CRS fixed stenosis)
A. 	B. 	C. 
Narrow curve: Instant ventilatory flow maintained, lung volume diminuished	**Hollow expiratory slope**: all instant ventilatory flows dropped	**Quasi-rectangular appearance:** the tip and the base of the loop are flattened

<u>Bronchomotorical tests</u> can be useful in diagnosing bronchial hiperreactivity in bronchial asthma. The bronchomotorical response is analyzed, based on modifications of MEVS, after administering aerosol.

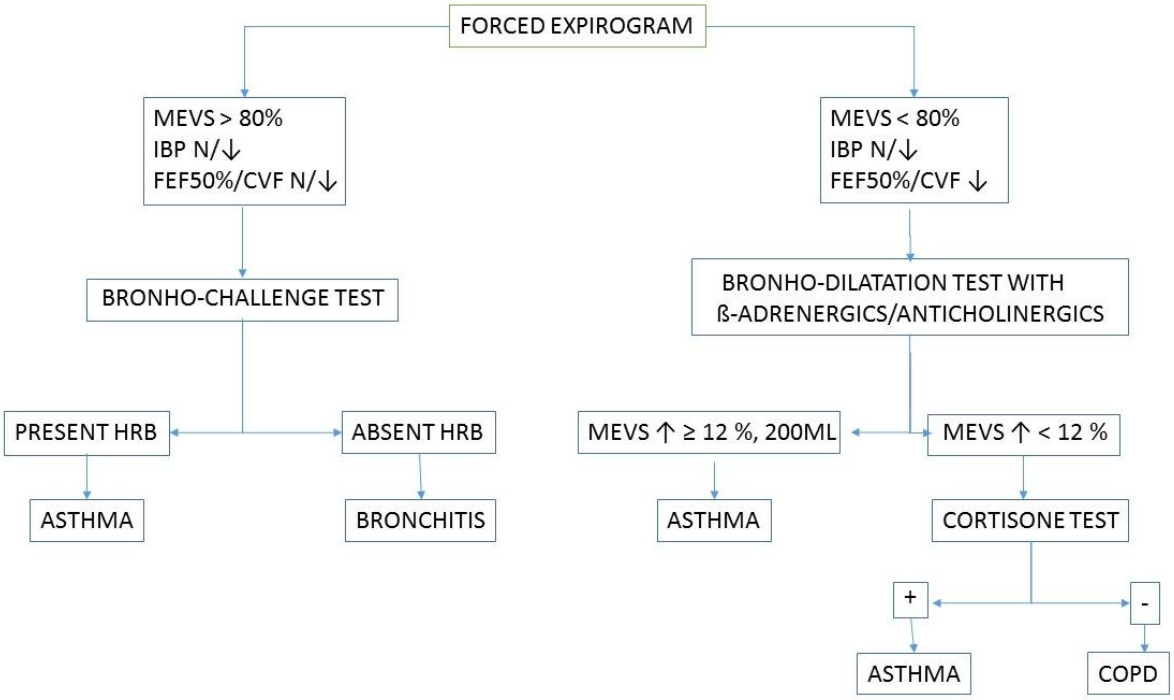


Figure 2. Algorithm in order to use bronchomotorical tests for emphasizing HRB.
(as in Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013))

- ***Tests of broncho-dilating (BD)***
  - Are carried aut for diagnostic purposes (emphasizing bronchial spasm and its reversability) or for therapeutical purposes (evaluating the efficiency of treatment by inhaling bronchodilators);
  - Administering by inhalation beta-andrenergic medication (**400 µg Salbutamol**) or parasimpaticolitic short-acting medication (**40 µg ipratropiu**);
  - positive test: **a significant rise of MEVS ≥ 12% and 200 ml compared to the initial value**,
  - in bronchial asthma, in the situation of a partial reversibility (8-11%), because of bronchial inflammation, the **corticosteroid test** is performed → oral corticotherapy is recommended for 7-10 days, or inhalatory for 3-4 weeks, then reevaluation through spirometry with bronchodilating test, where the significant rise of MEVS indicates a positive test.
- ***Tests of bronchial challenge***
  - These tests are used to identify, characterize and quantify the severity of the hyperreactivity of the airways (HRB);
  - They are performed for patients showing symptoms of bronchospasm, with normal spirometric parameters or unclear results after administering the bronchodilating test;
  - The agents used in tests of bronchial challenge can be classified according to their action mechanism:
    - direct stimuli: methacholine, histamine, prostaglandins, leukotrienes;
    - indirect stimuli: mannitol, adenosine, physical exercise, voluntary eucapnic hyperventilation, hypertonic saline solution;
  - prior to testing the following substances are to be administered:
  -

Short-acting Beta-agonists (inhaler)	*8 hours*
Long-acting Beta-agonists (inhaler)	48 hours
Anticholinergics	24 hours
Preparations with theophylline	12-24 hours
Antihistamines	72-96 hours
Anti-leukotrienes	24 hours
Products based on caffeine (cola, coffee)	6 hours
Corticosteroids	

Testing for metacholine:

Table 5. Contraindications to testing for metacholine	
Absolute	Relative
Myocardical infarction in the last 3 months Aortic aneurysm* Uncontrolled hypertension (high blood pressure) * FEV1< 50% out of the predicted (or < 1 l)	Pregnancy, confinement after birth Treatment with cholinesterase inhibitors VEMS < 60% aut of the predicted (or < 1,5 l) Mintal or physical disability
Notă: * these contraindications have been eliminated from the ATS-ERS criteria for per forming spirometry	

- patients are administered inhaler doses with ever growing concentrations of metacholine (for patients with HRB, one can notice obstruction of the airways in low doses of metacholine);
- administration can be made by breathing aerosol at current volume for 2 minutes or by using the technique of dosimetry with 5 breaths;
- in dosimetry with 5 breaths, the following concentrations of metacholine are to be used: 0 mg/ml → 0,065 mg/ml → 0,25mg/ml → 1mg/ml → 4mg/ml → 16mg/ml;
- positive test: **decrease of MEVS by 20% of the initial value**;
- the effect of metacholine on the airways is determined on the **response-dosis curve**, the severity of HRB is evaluated according to the concentration of metacholine determinig the lowering of MEVS by 20% (PC20%):
    - 0,02 – 1 mg/ml severe hyperreactivity,
    - 1 – 4 mg/ml moderate hyperreactivity,
    - 4 – 8 mg/ml slight hyperreactivity,
    - 8 – 16 mg/ml „border-line" hyperreactivity.

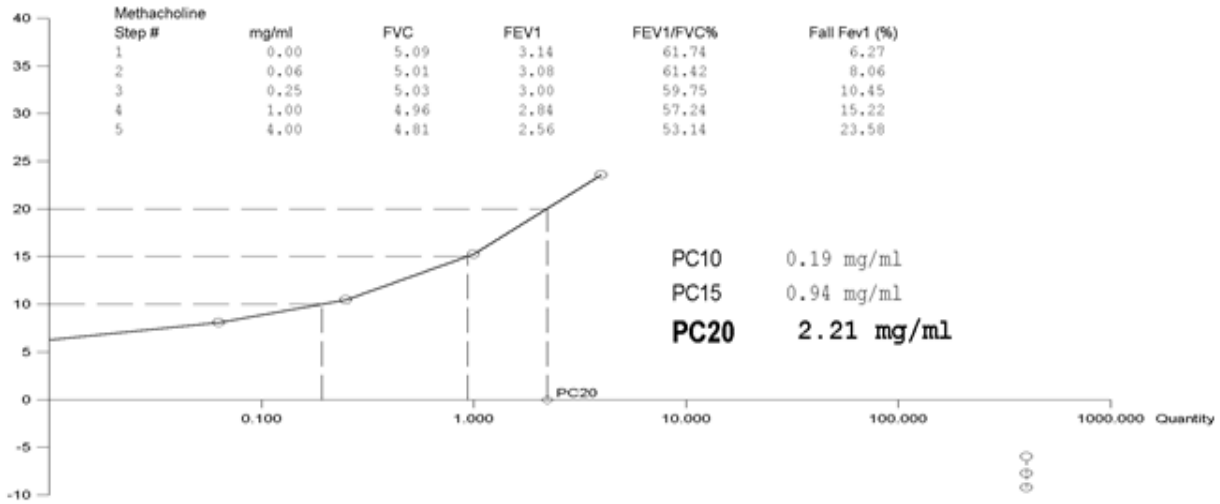


Figure 3. Dosis-response curve in administering cumulative doses of metacholine by the technique of dosymeria with five breaths.

(Adapted from Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013)

B. <u>Peak-flowmetria</u>

This is a method that <u>cannot replace spirometry</u>, but it is simple and useful in self-monitoring of asthma patients at home, both from the point of view of disease control, as from the point of view of response to treatment. The device called peakflowmeter measures **the maximum instantaneous peak expiratory flow (|PEF).** The PEF value i sone of the criteria for the functional defining of control zones for asthma patients, that is:

- *Controlled* (green zone): normal values, PEF > 80% from predicted or personal „best" with a circadian variation < 20%;
- *Partially controlled* (yellow zone): alert values, PEF of 50 – 80 % from predicted or personal „best" and circadian variations of 20-30%;
- *Uncontrolled* (red zone): emergency zone, values of PEF < 50% from predicted or personal „best" and a circadian variation > 30%.

C. Body-pletismography

This is a method of investigation that offers further information, more than spirometry, through which the forced inspiration and expiration flow is measured and thus the measurement of **absolute lung volume** (static) is made possible:

- **Residual functional capacity = *the air volume in the lungs after a normal expiration*,**
- **Total lung capacity = *the air volume in the lungs after a maximum inspiration*,**
- **Residual volume = *the air volume that cannot be exhaled from the lungs, not even after a maximum exhaling effort*.**

The technique is based on the *Boyle-Mariotte law* according to which the volume of air in a precinct varies in inverted proportion to the pressure it is exposed to, in isothermia (constant temperature). This is the most precise method of measuring the entire air volume in the lungs, estimating those spaces too, that are excluded from ventilation by the total obstruction of the bronchioles (emphysema bubbles), and also estimating the air in the hypoventilated territories.
Interpretation: the rise of CPT and VR

- normal values the 80 - 120% from predicted;
- slightly increased values 120 - 150% from predicted;
- moderately increased values150 - 180% from predicted;
- severely increased values > 180% from predicted.

Parenchymal restrictive ventilatory dysfunctions (pulmonary resections; increase of elastic recoil from: diffusive interstitial pneumopathy, pneumoconioses, colagenoses, sarcoidoses, tuberculosis, etc.) or extraparenchymal (pleural or thoracic wall pathology, neuromuscular diseases, limitation of diaphragm movement) is characterized by reduced lung volume, mainly CV and CPT (table 6).

Table 6. Changes in lung volumes in ventilatory dysfunctions
(Adapted from Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013)

Parameter	**Obstructive dysfunction**		**Restrictive dysfunction**		
	with hyperinflation	**with "trapped air *"**	**By parenchymal disorder**	**By extra-parenchymal limitation of inspire**	**By extra-parenchymal limitation of inspire and expire**
CV	N→↓	↓	↓	↓	↓
VR	↑↑	↑↑	↓	N→↓	↑
CPT	↑	N	↓	↓	↓
VR/CPT	↑	↑↑	N	↑	↑↑

Notes: N – normal;↑ – increased; ↓ – lowered; → – to; *trapped air – keeping supplementary air in the lungs at the end of forced expire by early collaboration of bronchioles.

Another parameter determined by this method is the resistance to flow of the airways (Raw), the indicator that evaluates the mechanical properties of the lungs. Approzimate normal values are about_0,05-0,22 KPa/L/s with an interindividual variability of 25%. This parameter, respectively the relations MEVS/CVF and $FEF_{50\%}$/CVF, helps define more functional images characteristic to obstructive syndromes in earlz stages of lung diseases (table 7).

Table 7. Functional images characteristic in early obstructive syndromes *(Adapted from Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013)*			
Parameters	**Patent obstructive syndrome**	**Discrete distal obstructive syndrome**	**Discrete central obstructive syndrome**
MEVS	**N →↓**	N	N
MEVS/CVF	**↓**	**N**	**N**
$FEF_{50\%}$ /CVF	**↓**	**↓**	**N**
Raw	**↑**	**N**	**↑**
Notes: N – normal;↑ – increased; ↓ – low; → – towards.			

II. Evaluation of lung gas exchange

This can be made by measuring the gas transfer factor of carbon dioxide through the capillary alveo membrane (DLco), and by determining the respiratory gases in the arterial blood (ASTRUP).

DLco furnishes data on the integrity of the capillary alveo membrane and the respiratory gases offer data on the ventilation/infusion rate in all pulmonary functional units. Some patients may display hypoxemia with a normal DLco (severe bronchial asthma), others may present normal values of arterial blood oxygen associated with a low DLco (pulmonary emphysema).

A. Determining gas transfer through the pulmonary capillary alveo membrane (pulmonary diffusion) for carbon monoxide (DLco)

This is the only investigation usually performed that can detect anomalies in pulmonary microcirculation. Tha gas transfer through the capillary alveo membrane depends on:

- *Characteristics of the membrane*: surface, thickness, functional efficiency;
- *Circulatory characteristics*: blood volume in capillaries, hemoglobin value (the Dlco value is corrected by the actual heoglobin concentration of the patient).

The transfer constant (Kco) = Dlco divided to the value obtained for alveo ventilation (VA), because Dlco is the product of the transfer rate by the capillary alveo membrane and VA.

Normal DLco values: 80-120% from predicted values based on age, height, sex and race. Decrease of Dlco is considered:

- light when > 60% prez.
- moderate when it is 40 - 60% prez.
- severe when < 40% prez.

Decrease of DLco can be seen in three major types of diseases:

- *Interstitial lung disease*: shrinking of the surface of the diffusion membrane, respectively decrease of the blood volume in pulmonary circulation, because of fibrosis of functional units;
- *Emphysema*: shrinking of surface of the alveo membrane because of the destruction of the alveolar walls;
- *Pulmonary vascular disease:* (pulmonary hypertension, pulmonary embolism, etc.) by reducing the volume of the vascular bed.

In table 8 the main disease are presented, where gas transfer through capillary alveo membrane is affected, respectively the pathophysiological mechanisms that can lead to these changes.

Table 8.Mechanisms of changhe of DL_{co} and derived parameters *(Adapted from Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013)*				
Diagnosis	**DL_{co} (%from pred)**	**K_{co} (%from pred)**	**VA (%from pred)**	**Mechanisms**
Bronchial asthma	↑	↑	N	Even distribution of infusion
Neuro-muscular disease	↓	↑	↓	Reduction of alveolar expansion
Pneumectomy	↓	N	↓	Loss of functional units
Pulmonary fibrosis	↓	N/↓	↓	Growth of elastic recoil ± alteration of capillary alveo membrane
Emphysema	↓	↓	N/↑	Alteration of capillary alveo membrane
HTP or pulmonary arteriopathies	↓	↓	N	Alteration of vascular bed

Figure 4 presents the current interpreting strategy for the results of pulmonary functional tests according to the guides.

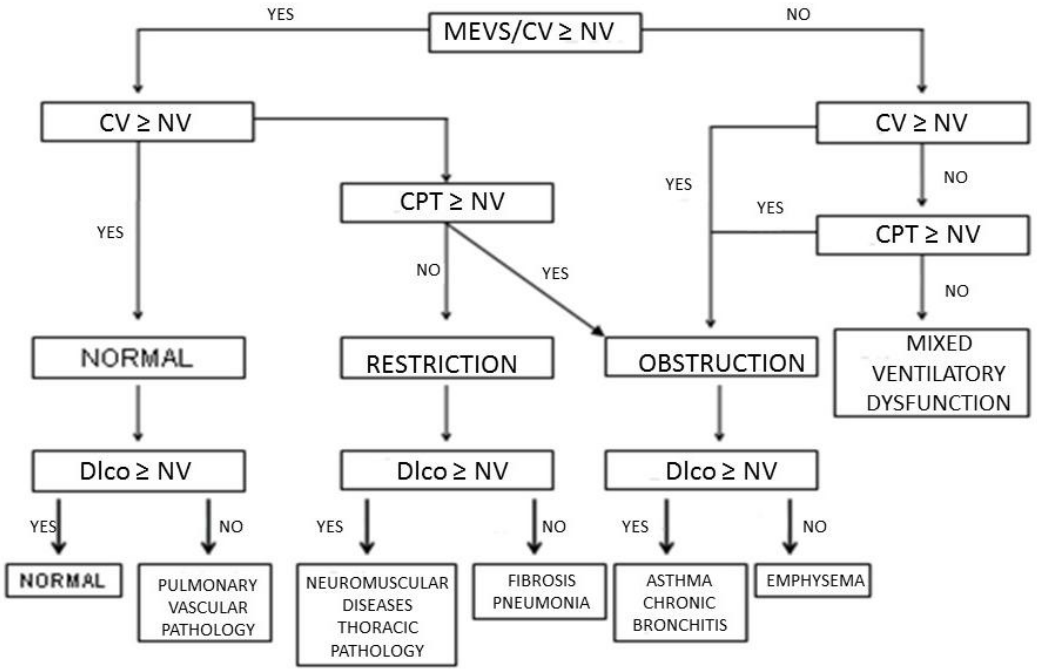


Figure 4. Interpreting algorithm for the results of pulmonary functional tests
(Adapted from Course of Pneumology for resident doctors, red. Voicu Tudorache, publ. Mirton 2013)

B. <u>Blood gas analysis in arterial blood</u> (ASTRUP)

It is performed by measuring the partial pressures of oxygen (PaO_2) and carbon dioxide (PaCO2) in the arterial blood. It is not an ideal method of monitoring, as it requires arterial puncture and provides intermittent data on the oxygenation level of the patient's blood,

Normal values: *PaO_2 = 80-100 mmHg*

$PaCO_2$ = 35-45 mmHg

For the calculation of the alveolo-arterial oxygen gradient ($PA\text{-}aO_2$) a simplified form of the alveolar gas equation is used:

$$P_AO_2 = 150 - 1{,}25 \times P_aCO_2$$

Normal values: *$PA\text{-}aO_2$ <15 mmHg (under 30 years)*, increasing by 3 mm Hg for every decade of life over 30 years.

Hypoxemia can be induced by the following pathophysiological mechanisms:

• decrease of inspired PO_2 level (high altitude);
• global alveolar hypoventilation (neuromuscular diseases, central regulation disorders);
• arterio-venous shunt (pulmonary atelectasis, pneumonia, pulmonary edema, congenital heart disease with shunt);
• ventilation / perfusion ratio disorder (diseases
respiratory tract, interstitial lung disease, alveolar disease, pulmonary vascular disease);
• due to diffusion alteration (special clinical situations).

Determining the cause of hypoxemia also depends on the value of $PaCO_2$, the calculation of the alveolo-arterial oxygen gradient ($PA\text{-}aO_2$) and the response to oxygen supplementation (see the chapter Respiratory Insufficiency). Table 9 shows the changes of the respiratory gases according to the mechanism responsible for hypoxemia,

Table 9.
Modification of arterial respiratory gases and alveolo-arterial oxygen gradient depending on the mechanism responsible for respiratory failure (hypoxemia)
(Adapted from the Pneumology Course for resident doctors under the editorial Voicu Tudorache, Publishing House Mirton 2013)

Mechanism	**P_aO_2**	**P_aCO_2**	**$P_{A\text{-}a}O_2$**
Global alveolar hypoventilation	↓	↑	↔
Mismatch of reports infusion - ventilation	↓	↔ ↓↑	↑
Diffusion disorders	↓	↔ ↓	↑
Arteriovenous shunt	↓↓	↔ ↓↑	↑↑

Note: ↔ – unchanged;↑ – grown; ; □ - low.

C. <u>Pulse oximetry</u>

It measures the saturation of blood hemoglobin with O_2 (SaO_2). Normal values: **95-97%.**

Benefits:

- is a non-invasive method, alternative to gasometry, which allows continuous monitoring of the patient.

Limits:
- there are discrepancies between PaO_2 and SaO_2, the pulse oximeter having a relatively low sensitivity to changes in partial pressure above 60 mmHg, a value that corresponds to a 90% saturation, due to the sigmoid type of the oxyhemoglobin dissociation curve;
- in the case of cutaneous peripheral vasoconstriction (low cardiac output or the use of vasoconstrictors), the pulse oximeter signal may be less accurate or not taken;
- the existence of other forms of hemoglobin (carboxyhemoglobin and methemoglobin) determines measured values of unreacted SaO2;
- does not provide data on $PaCO_2$ level, which can be modified even in the case of peripheral saturation $SaO_2 \geq 90\%$.

III. Effort tests

A. Cardiopulmonary testing during exertion

Testing requires complex equipment, laboratory with strict test quality control, as well as experienced and trained medical personnel. The test is also addressed to other devices and systems (cardio-vascular, muscular, metabolic), it has a synthetic character, but in evaluating the capacity to adapt to the effort of patients with pulmonary pathology it represents the **"gold standard"**.

Benefits:
- useful in differentiating dyspnea from pulmonary etiology, cardiac etiology or other causes;
- some incipient functional disorders can only be detected under conditions of physical request;
- the capacity to adapt to the effort of patients with clinically-functional pulmonary disorders is evaluated, as well as the limits of the physical training within the lung recovery program;
- it allows the deciphering of the main pathophysiological mechanism limiting the stress tolerance;
- provides data on the evolution and prognosis of chronic lung diseases, as well as on the results of pulmonary rehabilitation programs;

Method:
- the test is carried out on an ergometric bicycle or a rolling mat, with a loading on the ramp;
- from the analysis of the parameters measured directly or indirectly during the test, conclusions are drawn about the capacity to adapt to the effort of the cardiovascular and pulmonary apparatus, respectively the cardiovascular and / or pulmonary functional deficit is determined (a simplified algorithm for interpreting the results of the cardiopulmonary testing at effort is shown in Figure 5).

B. The 6-minute walk test

It is a simple test, easy to perform, which does not require complex equipment. It may be indicated to patients with chronic pulmonary pathology in view of the assessment of functional capacity, but it has proved useful in determining the hypoxia during the effort, being such a help in the decision on the administration of oxygen therapy at home

Method:
- before testing the following are noted: SaO2, heart rate, blood pressure, respectively level of dyspnea and fatigue validated on the Borg scale;

- on a 30 m long corridor, without obstacles, the patient is asked to go in a hurry step, while being timed;
- the most important parameter being followed is the distance traveled which is compared with the predicted value depending on a number of anthropometric parameters (age, height and weight) and sex, respectively the post-test values of the listed parameters.

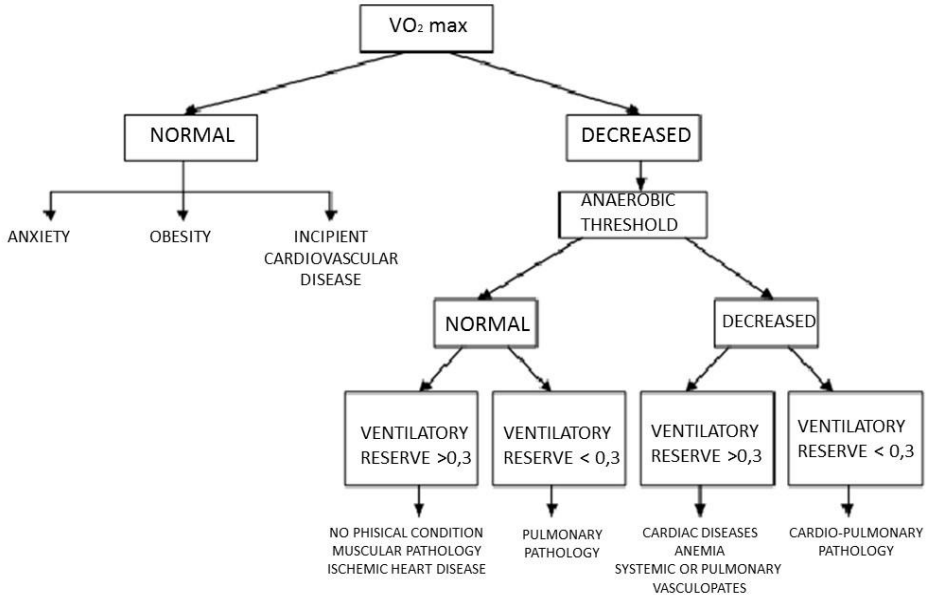


Figure 5. Diagnostic algorithm of the main factor for limiting stress tolerance.
(***Adapted from the Pneumology Course for resident doctors under the editorial Voicu Tudorache, Publishing House Mirton 2013)***

IV. Special tests

A. Evaluation of the respiratory muscles strength

The strength of the respiratory muscles is essential for maintaining adequate respiratory tract's ventilation and protection.

Muscle function is assessed by measuring the maximum inspiratory pressure (PImax = the lowest pressure during a forced obstacle sustained by adequate respiratory tract obstruction) and the maximum expiratory pressure (PEmax = the highest pressure developed during a forced expiration sustained by obstacle on the adequate respiratory tract).

Normal values: Pimax = - 50 cmH_2O women, - 75 cmH_2O men

The decrease of PImax causes restrictive dysfunctions of an extra-parenchymal nature, with only limitation of inspiration: neuromuscular diseases, diseases of the diaphragm, intercostal muscles, accessories, pulmonary emphysema by flattening the diaphragm, kyphoscoliosis, obesity. In this situation CPT is low and the VR modified is insignificant.

Normal values: Pemax = 80 cmH2O women, 100 cm H2O men

PEmax decrease: neuromuscular diseases, especially those with generalized muscular weakness, high cervical spine fractures, abdominal musculature innervation dysfunctions. In this situation VR is increased and associated with the inability to cough effectively.

In the case of a restrictive ventilatory dysfunction of neuromuscular nature, in the early stages of the disease, it is useful to determine the maximum direct ventilation (Vmax.dir).

Table 9. Evaluation of the respiratory muscles strength
(Adapted from the Pneumology Course for resident doctors under the editorial Voicu Tudorache, Publishing House Mirton 2013)

Clinical symptoms and signs that require the evaluation of the respiratory muscles strength	Clinical situations that require repeated measurements of the respiratory muscles strength
• Unexplained reduction of vital capacity • CO2 retention during waking or during sleep, specifically in the absence of severe obstruction of the respiratory tract • Orthopnoea • Dyspnea during bathing or swimming • Lack of air during the speech • tachypnea • Paradoxical movements of the abdomen or chest wall • Cough problems (with recurrent infections) • Generalized muscle weakness	• Known diseases that affect the respiratory muscles • Dyspnea installed after thoracic surgery (phrenic nerve paresis) • Progressive lung disease with possible impact on respiratory muscle function • Patients treated with high doses of corticosteroids • Patients undergoing specific programs of training of the respiratory musculature • Patients removed from mechanical ventilation

B. Measurement of bronchial inflammation

The measurement of bronchial inflammation is possible by 2 noninvasive techniques: by analyzing the sputum induced with hypertonic saline (only in specialized centers) or by determining the concentration of nitric oxide in the exhaled air (FENO).

Eosinophils raised in induced sputum (> 2%) or increased FENO in exhaled air (> 25 ppb at 50 mL / sec) are found in 75% of asthmatic patients, as well as 33% of patients with COPD or chronic cough. Studies show that eosinophilic bronchial inflammation is more associated with corticosteroid response than with asthmatic phenotype.

F_ENO:

- useful in diagnosing eosinophilic bronchial inflammation, response to corticosteroid treatment and monitoring of selected cases of severe refractory asthma;
- there is a minimal correlation in these patients between the FENO level and the lung functional tests;
- responds faster than spirometry to inflammatory changes due to exposure to allergens = marker more sensitive to disease;
- can also be measured at the level of the nasal cavities or sinuses, as a marker of nasal inflammation (rhinitis).

Interpretation:

- F_ENO <5 ppb: primary ciliary dyskinesia, cystic fibrosis, bronchopulmonary dysplasia;
- F_ENO = 25 - 50 ppb in adults: possible inflammation (from 20 to 35 ppb in children);
- F_ENO > 50 ppb: permanent eosinophilic inflammation (35 ppb in children).

In the case of smokers, the amount of NO in the exhaled air is reduced and the above interpretations cannot be taken into account.

Table 10. Interpretation of FENO values
(Adapted from the Pneumology Course for resident doctors under the editorial Voicu Tudorache, Publishing House Mirton 2013)

LEVEL	**LOW**	**NORMAL**	**INTERMEDIATE**	**GROWN**
EOZINOPHILIC INFLAMMATION	**Absence**	**Absence**	**Present but easy**	**significant**
ADULTS				
FE_{NO} (ppb)*	**< 5**	**5-25**	**25-50**	**> 50** *(or an increase of> 60% from a previous determination)*
Children < 12 ani				
FE_{NO} (ppb)*	**< 5**	**5-20**	**20-35**	**> 35**
** At a flow of 50 ml / sec*	**Important:** • Smoking? **Children:** • Primary ciliary dyskinesia (check NO nasal) • Cystic fibrosis • Chronic lung disease at the premature	**If symptoms occur** • Review of the diagnosis (To be considered: neutrophilic asthma, anxiety / hyperventilation, vocal cord dysfunction, gastro-oesophageal reflux, rhinosinusitis and heart disease. In addition to children: bronchitis, ENT and immunodeficiencies) **If no symptoms appear under treatment** • Patient compliant • Consider reducing the dose or giving up anti-inflammatory medication	**Interpretation based on the clinical aspect** **If symptoms appear under anti-inflammatory treatment:** • infection • Exposure to increased levels of allergens • Increased dose • Add LABA **In addition to children:** • Verification: - compliance - inhalation technique (For children, consider using MDI and spacer if the patient is using a dry powder device) **If no symptoms appear under treatment** • Do not change the dose of anti-inflammatory medication if the patient is stable	Consider **allergic asthma** if there is a history of the disease A positive response to inhalation or oral administration of steroids is likely **In addition to children:** • If there is objective evidence of respiratory tract obstruction reversibility, asthma is very likely **If symptoms appear under anti-inflammatory treatment:** • Verification: - compliance - inhalation technique -dose of medicines • To be considered - Exposure to levels - High in allergens - Imminent exacerbation or relapses - Steroid resistance (Rarely) **If no symptoms appear under treatment** • Do not change the dose of anti-inflammatory medication if the patient is stable

C. Forced oscillometry (FOT) technique

Pulse oscillometry

It allows passive measurement of pulmonary mechanics, using sound waves, generated using a microphone. Principle: sound waves (pressure waves) are superimposed on normal breathing, and changes in flow and pressure caused by external waves are used to calculate parameters that describe resistance to air flow, and the lung's reaction at different frequencies. This gives important information about regional inhomogeneity and pulmonary periphery. The lower frequency waves reach deeper into the alveoli, and those with high frequencies only up to large respiratory tract.

Benefits:

- requires minimal cooperation from the patient, which can easily be performed by patients who cannot perform spirometry (children, the elderly);
- it can differentiate small-track obstruction from large airway obstruction;
- is more sensitive than sirometry in the case of affecting the peripheral respiratory tract;
- measured parameters can detect early changes in lung function, especially at smokers, respectively loss of disease control at asthmatic patients.

Normal values: **R5 - R20 <0.03 kPa / L / s.**

BRONCHOSCOPY

Bronchial endoscopy or bronchoscopy is an endoscopic technique that allows real-time visualization and minimally invasive airway maneuvering. This technique has become indispensable for the pulmonologist.

Indications

- lung cancer
- hilum or mediastinal adenopathies,
- recurrent pneumonia in the same territory,
- interstitial lung disease,
- abnormal radiological aspects such as ascension of a hemidiaphragm, infiltrates of unspecified etiology, pulmonary atelectasis,
- suspicion of fistulas or post-traumatic lesions of respiratory tract,
- symptoms of unspecified etiology such as persistent cough, localized wheezing, stridor, dysphonia or hemoptysis.

Bronchoscopy also has therapeutic visas: extraction of foreign bodies, hemostasis of massive hemoptysis, resections of endotracheal / bronchial proliferative processes by laser therapy, electrocautery or cryotherapy, dilation of tracheal / bronchial stenosis, tracheal / bronchial stenting.

Contraindications

The only absolute contraindication is the patient's refusal to carry out this investigation. Relative contraindications are asthma attack, VEMS <25%, massive haemoptysis recently stopped, superior vena cava syndrome, myocardial infarction or recent stroke (<3 months), unstable angina, major arrhythmias, coagulation deficiency, etc.

Equipment

The bronchoscope can be optical (rarely used today in modern laboratories) or a video-bronchoscope that projects the images in real time and allows them to be stored.

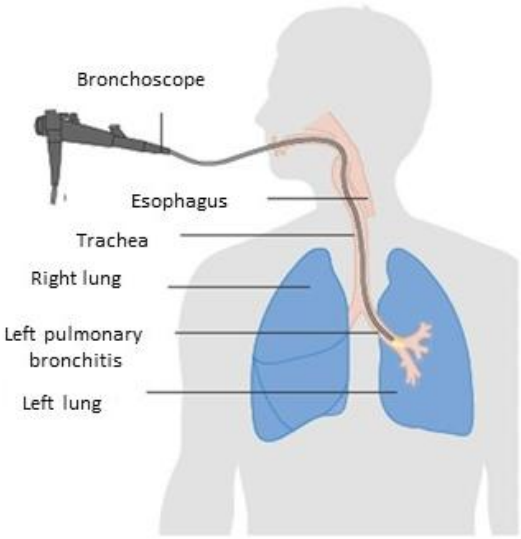
The instrumentation includes a series of simple accessories such as forceps, suction needles or brushes as well as complex tools used in interventional bronchoscopy.

Preparing the patient and working technique

Flexible (classical) bronchoscopy is most often performed under local anesthesia (Lidocaine) and requires good patient cooperation. The examination can be done orally, nasally or, where appropriate, through the tracheostomy orifice. The patient may be seated or examined in the dorsal decubitus.

Rigid bronchoscopy involves the use of a scope (straight metal tubes) for intubation, equipped with a light source, and the investigation is performed under deep sedation / general anesthesia.

The two flexible and respectively rigid techniques can be combined, to provide a good endobronchial access path for the flexible bronchoscope or instruments, and to obtain a better ventilation of these patients during the procedure.



Diagnostic techniques for sampling

Bronchial biopsy is performed under direct visualization, with flexible forceps that are introduced through the working channel of the bronchoscope. The procedure is followed by a histopathological examination of the samples.

Bronchial aspiration involves the instillation of 5-10 ml of saline solution in a territory, followed by its aspiration in a sterile container. The aspirated liquid will be analyzed cytologically and bacteriologically.

Brushing involves the collection of cells from the bronchial wall using a flexible brush that is inserted through the bronchoscope's working channel. The procedure is followed by cytological and bacteriological examination of the semple.
Transbronchial needle aspiration (TBNA) of the mediastinal adenopathies is performed by needles that are introduced through the bronchoscope's working channel, under direct visualization and allows puncture and aspiration of nodes or masses. It is followed by a cytological examination of the specimens.
Transbronchial biopsy (TBB) uses small forceps that are introduced through the bronchoscope's working channel, beyond visual control and allows to obtain the bioptic material from the periphery of the lung, that will be subjected to histopathological examination. It is indicated in establishing the etiology of peripheral masses or in the diagnosis of interstitial lung diseases.

Modern diagnostic techniques

Autofluorescence bronchoscopy is a technique that uses blue light to detect severe dysplasia or carcinoma in situ, undetectable in classical white light bronchoscopy. However, the procedure must be carefully interpreted due to the high number of false positive results.
Endobronchial ultrasound (EBUS) with TBNA associates a minimalized ultrasound probe placed at the tip of the bronchoscope, which allows the evaluation of the structures adjacent to the airway walls. This investigation is indicated for the determination of adenopathies / mediastinal messes etiology, lung cancer staging and diagnosis of loco-regional recurrences, peripheral pulmonary lesions biopsy, etc.

Complications

During the maneuvers, a number of complications may appear, such as desaturation, excessive coughing, laryngeal or bronchospasm, cardiac arrhythmias and exceptionally acute pulmonary edema or myocardial infarction. Transbronchial biopsy can very rarely lead to major complications such as pneumothorax or massive hemorrhage, requiring surgery in some cases.

Thus, bronhoscopy is a relatively safe method of respiratory tract exploration, which requires only local anesthesia and allows visualization and sampling of bronchial tree, in a short time.

References

1. Pneumology course for resident doctors under the editorial Voicu Tudorache, Mirton 2013
2. Murray & Nadel's Textbook of Respiratory Medicine, 6th ed., 2016 Saunders, Elsevier
3. ERS Handbook of Respiratory Medicine 2nd Edition, publisher European Respiratory Society, 2017
4. Ruppel's Manual Of Pulmonary Function Testing, 11th edition, Carl D. Mottram, 2018
5. Interpretation of Pulmonary Function Tests, A Practical Guide, Robert E. Hyatt, Paul D. Scanlon, Masao Nakamura, Third Edition, 2000
6. Bogdan M (ed.). Pneumology, "Carol Davila" University Publishing House, Bucharest, 2008.
7. Impulse oscillometry: The state-of-the-art for long function testing, Koundinya Desiraju, Anurag Agrawal Lung India. 2016 Jul-Aug; 33 (4): 410-416. doi: 10.4103 / 0970-2113.184875
8. News in thoracic, diagnostic and therapeutic endoscopy. Under network. : Ruxandra Ulmeanu, Florin Dumitru Mihălțan, Ioan Cordoș, Dan Ioan Ulmeanu. Bucharest. "Carol Davila" University Publishing House, 2009. ISBN 978-973-708-405-7
9. Bronchoscopy and central airway disorders: a patient-centered approach. Henri Colt, Septimiu Murgu. Elsevier Saunders. ISBN 978-1-4557-0320-3
10. Atlas of Flexible Bronchoscopy. Pallav Shah. CRC Press. ISBN 978-0-340-96832-1
10. Atlas of Flexible Bronchoscopy. Pallav Shah. CRC Press. ISBN 978-0-340-96832-1

3. MICROBIOLOGICAL DIAGNOSIS IN RESPIRATORY INFECTIONS

Pneumonia, which has been labeled "the friend of the elderly", continues to be the most common death-causing infection in the world. Sir William Osler stated in 1901 in the Principles and Practice of Medicine: "the most widespread and fatal of all acute diseases, pneumonia, is now the captain of the death tolls."

Microorganisms reach the lower respiratory tract by inhalation, aspiration or through the bloodstream. Immunocompetent subjects are susceptible to infections caused by pathogens that possess adhesins, through which germs attach to specific receptors in the respiratory epithelium. Those with altered defense capabilities, for example those immunocompromised, with viral infections in the near past or with cystic fibrosis may develop opportunistic infections (Pneumocystis jirovecii causing pneumonia in AIDS patients).

The respiratory tract has a limited number of ways to respond to infections: lobular pneumonia, bronchopneumonia, interstitial pneumonia, pulmonary abscess, pleural empyema. Viral infections (respiratory syncytial virus, parainfluenza) and bacterial infections, secondary to a viral respiratory infection (after measles), predominate in childhood. Bacterial etiologies are more common than viral for adults, conditioned by occupation (Coxiella burnetii), contact with certain animals (Brucella spp), trips to certain geographical areas (Coccidioides immitis), alcoholism, vagrancy.

Increasing problems raise the treatment of infections for those with HIV (cytomegalic virus, Pneumocystis jirovecii, Mycobacterium spp.), those with organ transplants (cytomegalic virus, Aspergillus, Nocardia, M. tuberculosis), as well as nosocomial infections (gram negative bacteria: Klebsiella, Serratia, P.aeruginosa).

The diagnosis of respiratory infections is made by correlating the epidemiological elements (anthrax - contact with herbivores, exposure to wool; brucellosis - consumption of unpasteurized milk; psittacosis - exposure to birds, parrot, turkey, pigeon; Legionnaires' disease - inhalation of aerosols from air conditioners; tularemia - contact with infected animals, rabbit, fox; histoplasmosis - exposure to bat waste, birds), clinical data (condensation syndrome, abolition of respiratory murmur, etc.) and paraclinical investigations (imaging, microbiology, etc.). In general, the diagnosis of respiratory disease is not difficult, but laboratory identification of etiological agents often raises problems.

Efforts to determine the precise etiology of respiratory disease are justified by the fact that it allows the clinician to narrow the antibiotic spectrum, use fewer pharmacological agents, reduce the patient's exposure to possible side effects and reduce the occurrence of antibiotic resistance. At the same time, less suspected pathogens can be identified, which are not included in the scope action of the "empirical" initial therapy.

Table 1. Etiological agents involved in respiratory pathology:

Commonly identified bacteria:	***Bacteria rarely encountered:***	***Viruses***
Streptococcus pneumoniae Staphylococcus aureus Haemophilus influenzae Bacteroides spp. Fusobacterium spp. Peptostreptococcus spp. Peptococcus spp. Prevotella spp. Enterobacteriaceae Escherichia coli Klebsiella pneumoniae Enterobacter spp. Serratia spp. Pseudomonas aeruginosa Legionella spp.	Acinetobacter Actinomyces Bacillus spp. Moraxella catarrhalis Campylobacter fetus Eikenella corrodens Francisella tularensis Neisseria meningitidis Nocardia spp. Pasteurella multocida Proteus spp. Pseudomonas pseudomallei Salmonella spp. Enterococcus faecalis Streptococcus pyogenes	Virus gripal A Virus gripal B Virus sincițial respirator Metapneumovirus uman Adenovirus tip 4 și 7 Rhinovirus Enterovirusuri Virus ECHO Virus Coxsackie Virus Epstein-Barr Virus citomegalic Virus varicelo-zosterian Virus parainfluenza Virus rujeolic Virus herpes simplex Hantavirus Virus herpetic uman 6 Coronavirus (SARS)
Fungi	***Other agents that cause pneumonia:***	***Parasites***
Histoplasma capsulatum Coccidioides immitis Rhizopus spp. Absidia spp. Mucor spp. Cunninghamella spp. Aspergillus spp. Candida spp.	Coxiella burnetii Rickettsia rickettsiae Mycoplasma pneumoniae Chlamydophila psittaci Chlamydia trachomatis Chlamydophila pneumoniae (TWAR) Mycobacterium tuberculosis Micobacterii nontuberculoase M. abscessus M. avium complex M. kansasii M. chelonae M. fortuitum M. xenopi M. simiae M. scrofulaceum M. malmoense	Ascaris lumbricoides Pneumocystis jirovecii Strongyloides stercoralis Toxoplasma gondii Paragonimus westermani

Pathological samples

For the microbiological diagnosis of lower respiratory tract infections the following can be examined:

a. Samples contaminated with the upper respiratory tract microbiota: sputum, naso-pharyngeal swab, naso-pharyngeal aspirate, hypopharyngeal, through endotracheal tube, through simple bronchoscopy. Aspirate through the tracheostomy cannula is frequently contaminated with germs from the external environment.

b. Samples that avoid oro-pharyngeal contamination: transtraheal aspirate, bronchoscopy aspirate with protected catheter, transbronchial biopsy, lung biopsy; pleural aspirate; blood cultures.

Samples with oro-pharyngeal contamination pose problems in interpreting the significance of the isolates: if the pathogen-conditioned organisms detected have clinical significance or represent contamination flora , if a pretentious pathogen is not masked by the growth of the contaminants. Primary pathogens, tuberculosis bacilli, pathogenic fungi, Mycoplasma pneumoniae, Chlamydia spp., Coxiella burnetii, Legionella pneumophila have clinical significance regardless of the sample in which they were detected.

Microscopic examination

From the taken product and possibly fluidized, there are 4 smears, which are colored as follows:

- a smear with blue methylene for general appreciation of the elements
- a Gram colored smear with for appreciation of the gram-positive and gram-negative flora
- a Ziehl-Neelsen colored smear for acid-alcohol-resistant bacilli
- a colorful May-Grunwald-Giemsa smear for cytology.

A number of microorganisms cannot be detected by Gram staining: Legionella, Mycoplasama, Chlamydia and Chlamydophila species.

Current samples:

1. Sputum

It is taken from the hospitalized, cooperative patient, with spontaneous, deep and supervised cough, before the initiation of antimicrobial therapy. The patient must understand the difference between “spitting” and “expecting”. The sample should not consist mainly of saliva. Samples taken in a sterile, wide-mouth, airtight container should be sent immediately to the laboratory for examination within one hour of collection.

Sputum examination should include references to appearance, color, quantity, consistency and odor. "Rust" sputum suggests pneumococcal pneumonia, "jelly" type (dark red, mucoid) pneumonia produced by Klebsiella pneumoniae while "aqueous" sputum occurs in atypical pneumonias. A fetid sputum suggests the presence of mixed anaerobic infection - aspiration pneumonia.

In order to increase the value of the sputum examination we must follow the ratio between the number of neutrophils to epithelial cells (objective x100), to reduce oropharyngeal contamination. The ratio between the actual pathological product (objectified by the number of inflammatory cells, the presence of fibrin) and the oropharyngeal contamination (objectified by the number of squamous epithelial cells) allows establishing quality thresholds. Samples containing 25 or more neutrophils and 10 or fewer epithelial cells are taken into account.

Sputum examination is not suitable for the correct detection of the following germs: Pneumocystis jirovecii, Aspergillus, Candida albicans (due to insufficient mobilization of these pathogens in the bronchopulmonary outbreak), Legionella (due to antagonization by the oropharyngeal microbiota).

Recommended culture mediums are: blood agar, chocolate blood agar and a lactose differentiated medium.

1) Nose-pharyngeal swab

It is only indicated for the diagnosis of lung infections with primary pathogens, microorganisms that do not belong to the oro-pharyngeal microbiota.

2) Gastric aspirate

It is performed with an empty stomach, it is indicated for detection of tuberculosis bacilli, especially in children.

3) Pleural aspirate

Parapneumonic pleural effusion occurs in 20% - 40% of patients with pneumonia. The incidence of pleural effusion associated with pneumonia varies depending on the etiological agent: 40% - 50% pneumococci, 50% - 70% gram-negative bacilli, 95% group streptococci A. Examination of the pleural fluid has a particular value in determining the need for drainage and in order to differentiate other causes of pulmonary infiltrates, which may mimic bacterial pneumonia (pulmonary tuberculosis, various tumors, pulmonary embolism, collagenosis).

In the case of transudate, the liquid has a serous appearance, the number of leukocytes is below 10,000 / mm3, pH above 7.2, proteins below 3 g / dl, LDH below 200 IU / l, glucose above 60 mg / dl. When it is an exudate, the pleural fluid is cloudy, with leukocytes over 50,000 / mm3, pH below 7.2, protein over 3 g / dl, LDH over 200 IU / l, glucose below 60 mg / dl.

4) Suction through the tracheostomy hole

The tracheostomy and the cannulation induce an inflammatory process over which the early colonization with microorganisms aspirated from the external environment as a result of the upper airway filter being disrupted and the muco-ciliary transporter being altered.

5) Transtraheal aspirate

It is an invasive method, the sampling being the competence of the pulmonologist. It has the following indications: a) when the sputum or other samples do not give conclusive results due to the oropharyngeal contamination (anaerobic bacteria, C.alibicans) or b) to exclude an infectious process in pneumopathies of other etiology (neoplasm, pulmonary embolism).

6) Transthoracic pulmonary aspirate.

Transthoracic aspiration obtains uncontaminated samples directly from the lung parenchyma. It has the following indications: a) non-usual lung infections of the adult or to the immunocompromised ones, b) nodular lung lesions suspected of malignancy with associated infection, c) severe diseases in the non-expectorating child. In HIV patients with focal or diffuse pulmonary infiltrates, pulmonary pathogens were detected in the lung aspirate in a proportion of 50-80%: Legionella, P. jirovecii, mycobacteria, opportunistic fungi, nocardias.

7) Bronchoscopic samples

Sampling through protected devices has the advantage of avoiding oropharyngeal contamination and reducing the proportion of false positive results. The association of transbronchial biopsy with endobronchial brushing and bronchoalveolar lavage improves the efficiency of the investigation.

8) Blood cultures

Performed systematically, correctly, in the first days of evolution of an acute pulmonary process, before the initiation of antibiotic therapy are positive in 30% of the patients with pneumonia.

9) Serological tests

In a number of etiologies benefiting from antibiotic therapy (M. pneumoniae, C. pneumoniae, C.psittaci, C. trachomatis, Coxiella burnetii) the results of the microbiological examination are late. It is preferred to test the serums in dynamics (acute serum and convalescent serum) with a fourfold increase of the titer. Titration of IgM class antibodies after the first week of the disease allows diagnosis, including in viral etiologies.

10) Antigen detection

In the last two decades, the fluorescent antibody technique has been increasingly used to detect antigens from respiratory secretions to diagnose infections caused by S. pneumoniae, Pneumocystis (80% sensitivity and 90% specificity).

Detection of antigens in the urine and not in the blood or sputum has become a useful diagnostic way in infections caused by L. pneumophila. It has a sensitivity of 80-95% and a specificity estimated at 99%. It should be noted that antigenuria persists for weeks to months after antibiotic therapy.

11) PCR technique

The PCR technique has a number of obvious advantages: very small amounts of material from potential pathogens can be identified, it is not influenced by previous antibiotic therapy and the results are rapid. It is reserved for the diagnosis of infections with M.tuberculosis and Legionella sp. The sensitivity is 63% and the specificity 99%. The problem of false positive results remains. PCR was positive in 70% of the subjects with previous exposure to M. tuberculosis but without active disease.

12) Pulmonary biopsy.

The major indication refers to the diagnosis of pulmonary disorders in immunocompromised patients. The proportion of detection of the etiological agent (opportunistic bacteria and fungi, mycobacteria, actinomycetes, P. jirovecii) varies between 50 and 90%, higher than the detection by bronchial biopsy.

Bibliography:

1. Goering RV, Dockrell HM, Zuckerman M, Roitt IM, Chiodini PL. Mims' Medical Microbiology. 2013 Elsevier
2. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas and Bennett's Prin ciples and Practice of Infectious Diseases. 2010 Churchil Livingstone Elsevier
3. Buiuc D, Neguț M. Tratat de microbiologie clinică. 2008 București Ed. Medicală

4. RESPIRATORY FAILURE

1. Definition

Respiratory failure (RF) is a pathological condition defined by impaired pulmonary gas exchange, decreased oxygenation of venous blood, decreased elimination of carbon dioxide or both, which is accompanied by changes in the partial pressure of respiratory blood gases.

Hypoxemia, $PaO_2 < 60$ mmHg
Hypercapnia, $PaCO_2 > 45$mmHg

The diagnosis is based on blood gasometry.

2. Classification

• Depending on the installation mode:
- Acute
- Chronic
- Exacerbated chronic

• Depending on the severity: - latent, with manifestations only at exertion (light, medium, severe)
- manifest, with manifestations at rest

• Depending on the gases whose exchange is affected:

Table. 1 Classification of respiratory failure by the altered blood gases		
Partial (type I) or pump insufficiency	PaO2< 60 mmHg	hypoxemia
	PaCO2 < 45 mmHg	normo/hypocapnia
Global (type II) or pulmonary insufficiency	PaO2< 60 mmHg	hypoxemia
	PaCO2 > 45 mmHg	hypercapnia

- Depending on the severity of the gas alteration:

	Hypoxemia	*Hypercapnia*
Mild	95-60 mmHg	45-50 mmHg
Moderate	60-45 mmHg	50-70 mmHg
Severe	<45 mmHg	>70 mmHg

3. Ethiopathogenesis

The hypoxemic respiratory failure is based on four pathophysiological mechanisms:

- Global alveolar hypoventilation
- Alteration of ventilation / infusion ratio (V / Q)
- Disorder of alveolo-capillary diffusion
- The right-left intrapulmonary shunt

I. Alveolar hypoventilation

Characterised by decreased amount of air that ventilates the lungs and participates in gas exchange, with the decrease of PaO2 below 60 mm Hg and the increase of PaCO2 above 45 mm Hg. The pressure gradient of alveolo-arterial oxygen (PA-aO2) remains unchanged (normal: 5-15 mm Hg). Table 2 shows the main causes of hypoventilation.

It can be treated by administration of oxygen in high concentration.

! Keep in mind that the administration of pure oxygen is contraindicated because it can induce respiratory arrest by canceling the hypoxemic stimulus from the carotid sinus, when the respiratory center is depressed by hypercapnic acidosis.

Table 2. Causes of alveolar hypoventilation

Adapted after Pneumology Course for resident physicians under Voicu Tudorache, Mirton 2013

Disfunction of respiratory centers	Anesthesia, sedatives, alcohol, dyselectrolithemia, hypoglycemia, myxedema, brain tumors, CNS infections, craniocerebral trauma, stroke, intracranial hypertension, sleep apnea syndrome (SAS)
Peripheric neurological diseases	Poliomyelitis, Amyotrophic Lateral Sclerosis, Gulian Barre Sd.
Respiratory muscle abnormalities	Curara, arsenic, aminoglycosides, dyselectrolithemia, botulism, tetanus, muscular dystrophy, myasthenia gravis
Upper airway diseases	Polyps, tonsil hypertrophy, laryngitis, laryngeal edema, stenosis-compression, tracheomalacia, foreign bodies
Thoracic, pleural diseases	Trauma, thoracoplasty, kyphoscoliosis, scleroderma, achylopoietic spondylitis, obesity, ascites
Pulmonary diseases	COPD, Severe infections, Pulmonary thromboembolism, Atelectasis, Acute pulmonary edema

II. Alteration of ventilation / infusion ratio (V / Q)

It is the ratio that defines the relationship between alveolar ventilation and alveolar irrigation within the pulmonary unit. Normal values V / Q = 0.8-1. It is characterized by modified PA-aO2. It can be corrected by administering oxygen in high concentration.

V = (VC - Dead space) x frequency = (500-150) x 12 = 4200 ml / min
Q: 5 L / min = right ventricular flow

Causes:
• V / Q> 1: ventilated but not irrigated alveoli: pulmonary emphysema, heart failure, pulmonary embolism, controlled mechanical ventilation;
• V / Q <1: irrigated but hypoventilated alveoli: COPD, atelectasis, pneumonia, bronchial asthma, acute pulmonary edema, acute respiratory distress syndrome (ARDS).

III. Alveolo-capillary diffusion disorder
The diffusion capacity for oxygen through the alveolo-capillary membrane is 15-20 ml O2 / mmHg and the transit time of the alveolar capillary is 0.75sec. The severity of the damage depends on: the difference of partial gas pressure between the alveolar air and the pulmonary capillary, the contact time of the blood in the capillary with the alveolar air, the size of the gas exchange surface and the thickening of the alveolo-capillary membrane.
It can be corrected by administering oxygen in high concentration. Breathing in oxygen-poor atmosphere and physical exertion precipitate its installation.
Causes: pulmonary and interstitial edema, pulmonary thrombembolism, diffuse pulmonary hemorrhage, sclerosis and pulmonary fibrosis.

IV. Intrapulmonary shunt
It does not respond to oxygen administration, even in high concentrations.
Causes: pulmonary arteriovenous fistulas, atelectasis, pulmonary edema, pneumonia.

4. Diagnosis

The main symptoms and elements of clinical examination of hypoxia and hypercapnia are shown in tables 3 and 4.

Table 3. Clinical manifestations of hypoxia
Adapted from the Pneumology Course for resident physicians under Voicu Tudorache, Mirton publishing house 2013

	Acute hypoxemia	Chronic hypoxemia
Respiratory and cardiovascular system	Dyspnoea, tachypnea, high blood pressure tachycardia / bradycardia with hypotension, acute pulmonary heart, arrhythmias	Chronic dyspnea, chronic pulmonary hypertension, chronic pulmonary heart
Nervous system	Agitation, motor instability, alterated state of mind	Drowsiness, attention and personality disorders
Clinical exam	Cyanosis	Cyanosis, polyglobelia, hypocratic fingers

Table 4. Clinical manifestations of hypercapnia *Adapted after Pneumology Course for resident physicians under Voicu Tudorache, Mirton 2013*		
	Acute	**Chronic**
Nervous system	Hypercapnic encephalopathy, carbonarcosis (coma)	Chronic intracranial hypertension, papillary edema of the eye
Cardiovascular system	Tachycardia, arrhythmias, BP disorders	Very few signs
Respiratory system	Dyspnea, tachypnea	

5. Paraclinical examination

Pulse oximetry (figure 1):
• Detects pulsatile blood flow, HbO2 and HbH
• Estimates arterial saturation of Hb
• Critical threshold: 90%
• Sources of error: hypotension, HbCO, modified nails

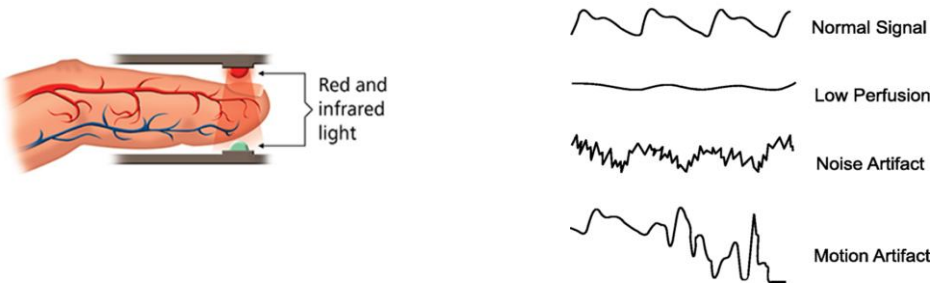


Figure 1. The principle of pulse oximetry and signal types

The suggestive value of hypoxemia at pulse oximetry (SaO2 ≤ 90%, due to the limitations of the measurement technique) must always be confirmed by gasometry.

Arterial gasometry: confirms the diagnosis.
It allows the assessment of the state of the acid-basic balance, the oxygenation status, the electrolyte balance.
The normal values and the significance of the obtained acid-basic parameters are as follows:
- The current pH (v.n. = 7.35-7.45) represents the pH of the examined blood;
- standard pH (vn = 7.35-7.45) and standard bicarbonate (vn = 23-27 mEq / l) indicate the value of these parameters under standard conditions (pCO2 of 40 mmHg, 37oC, saturation Hg with O2 of 100 %);
- pCO2 (v.n. = 38-42 mmHg) is the partial pressure of carbon dioxide in the examined blood;
- buffer bases (v.n. = 48-52 mEq / l) represent the sum of all buffer anions capable of accepting protons (bicarbonate, hemoglobin, protein, phosphates) present in one liter of blood;

- the excess bases (v.n. = ± 2 mEq / l) represent the deficit (when the value is negative) or the excess of bases (when the value is positive) compared to the normal value of the buffer bases; the value of BE is of clinical importance being used in the calculation of the need for a bicarbonate solution in the treatment of acid-basic imbalances according to the formula 0.3 x Gc (kg) x BE;
- the current bicarbonate (v.n. = 20-24 mEq / l) represents the value of the bicarbonate in the examined blood;
- Total CO2 (ie = 24-27 mEq / l) is the sum of the actual bicarbonate and the amount of CO2 dissolved in the plasma, expressed in mEq / l and obtained by the formula pCO2 x 0.3.

A simple way to assess the type of acid-basic imbalance is to use the nomogram (fig. 2), and a simplified interpretation algorithm is the following:

1. A modified pH is suggestive of the type of imbalance, namely acidosis (all conditions that tend to lower blood pH either by increasing acids or by lowering bases) or alkalosis (all conditions that tend to increase pH by opposite phenomen)
2. Modification of only one of the factors, metabolic or respiratory, denotes an unbalanced imbalance due to the nature of the modified factor;
3. If both factors are altered concordantly (in the same sense), the imbalance is compensated and is metabolic in nature if the sense of change of bicarbonate is similar to that of pH, or of a respiratory nature when the sense of change of bicarbonate is different from that of pH;
4. If both factors are changed discordantly (in the opposite direction), the imbalance is mixed. However, starting from the ones presented above, the correct interpretation is the one that corresponds to the *clinical context* and the *limitations regarding compensation* (table 5).

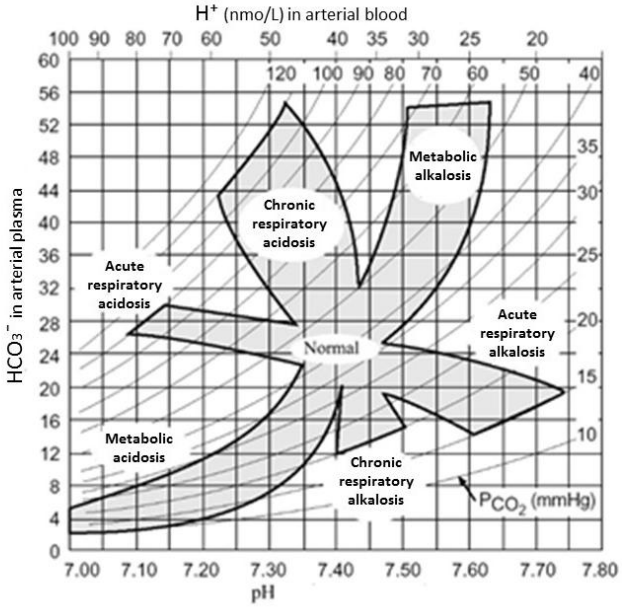


Figure 2 Acid-basic normogram (shaded areas represent 95% of the limits in which simple acid-basic imbalances are compensated)

Table 5. Prediction of compensation respnse of simple acido-basic alterations

Imbalance	Prediction of compensation	Compensation limit
Respiratory Alcalosis		
Acute	$[HCO_3^-]$ ↓ with 2 mEq/l for 10 mmHg ↓ of $PaCO_2$	$[HCO_3^-]$ >18 mEq/l
Chronic	$[HCO_3^-]$ ↓ with 5 mEq/l for 10 mmHg ↓ of $PaCO_2$	$[HCO_3^-]$ >12-15 mEq/l
Respiratory acidosis		
Acute	$[HCO_3^-]$ ↑ with 1 mEq/l for 10 mmHg ↑ of $PaCO_2$	$[HCO_3^-]$ < 30 mEq/l
Chronic	$[HCO_3^-]$ ↑ with 4 mEq/l for 10 mmHg ↑ of $PaCO_2$	$[HCO_3^-]$ < 45 mEq/l

In figures 3 and 4 are summarized the clinical algorithms for diagnosing the causes of hypoxemia, respectively hypercapnia.

Depending on the changes in the parameters of gasmetry we can predict the type of respiratory failure by its installation mode:

- Acute RF: PaO2 <50 mmHg, PaCO2> 60-70 mmHg, pH <7.35, HCO3 <29-30 mEq / l;
- Chronic IR: PaO2 <50 mHg, PaCO2> 60-70 mmHg, pH> 7.35, HCO3> 27-30 mEq / l;
- Chronic exacerbated RF: PaO2 <50 mmHg, PaCO2> 60-70 mmHg, pH <7.30, HCO3> 35-39 mEq / l.

Other investigations are: functional tests, chest radiography, chest tomography, HRCT (high resolution tomography), echocardiography, EKG, hemolysogram, blood glucose, urea, creatinine. These may direct the clinician to identify the cause of respiratory failure.

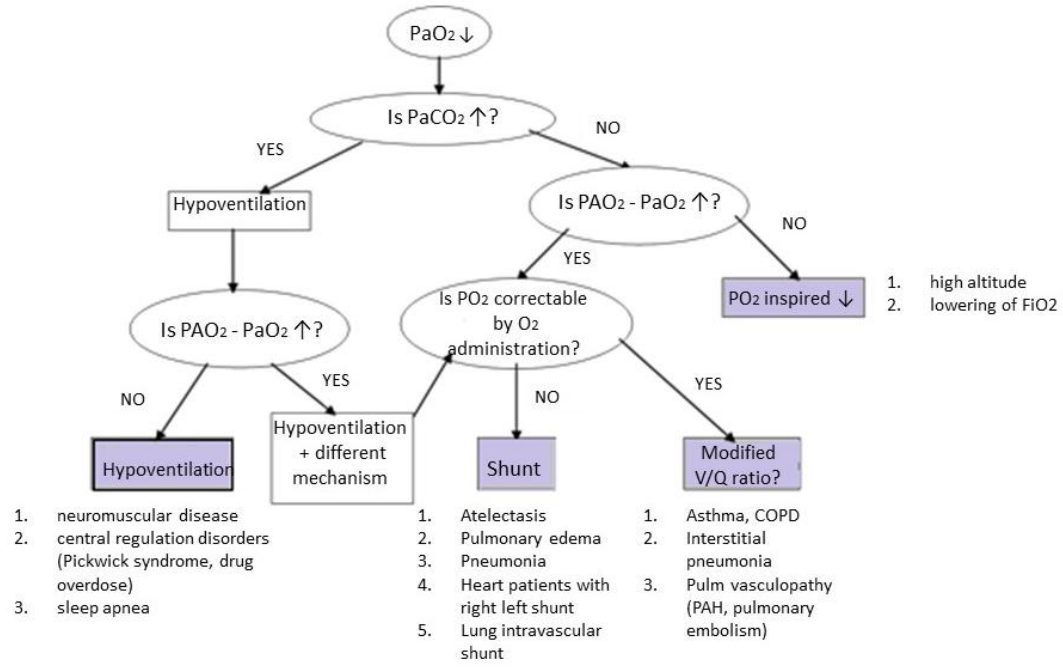


Figure 3. Diagnostic algorithm of the patient with hypoxemia.
(Adapted from the Pneumology Course for resident physicians under Voicu Tudorache, Mirton 2013)

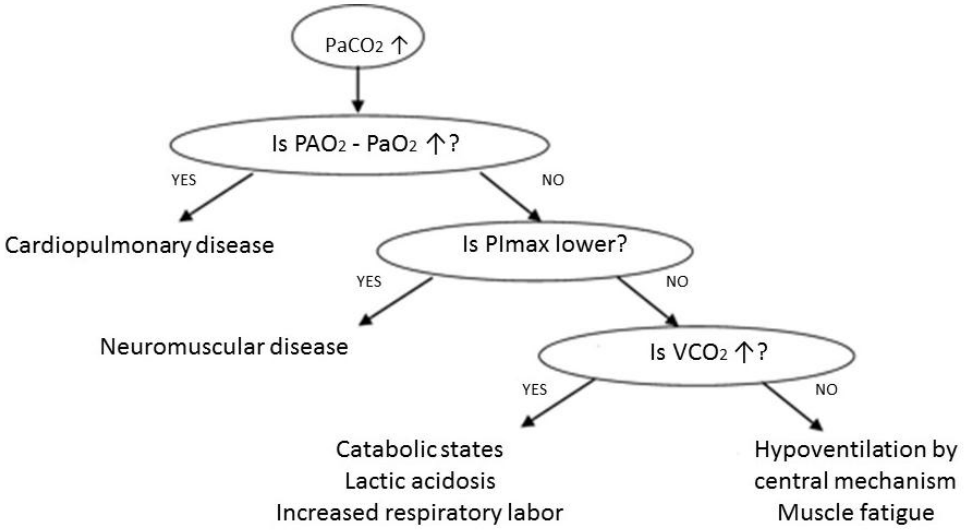


Figure 4. Diagnostic algorithm of the patient with hypercapnia.
(Adapted from the Pneumology Course for resident physicians under Voicu Tudorache, Mirton 2013)

5. Complications

Systemic complications due to the presence of respiratory failure:

• Bronchopulmonary: pulmonary embolism, diffuse interstitial fibrosis (post-SDRA),
• Cardiovascular: arrhythmias, hypotension, decreased cardiac output, CPC, HTP,
• Gastrointestinal: bleeding,
• Kidney: acute kidney injury,
• Hematological: anemia, polyglobalgia, CID,
• Nutritional: protein-caloric malnutrition,
• Musculoskeletal: contractile dysfunction and insufficiency of the respiratory muscles (in obstructive diseases, restrictive diseases, neuromuscular diseases).

Complications secondary to the treatment of respiratory failure:

• Secondary of the specific instrumentation in the ATI service: barotrauma in case of invasive ventilation (pneumothorax, pneumomediastin, pneumoperitoneum, subcutaneous emphysema),
• Infectious: nosocomial pneumonia, VAP (ventilator associated pneumonia)

6. Evolution and prognosis

Mortality varies according to etiology. Patients under the age of 60 have a better survival rate than the elderly. About 2/3 of the patients surviving an episode of respiratory failure show a deterioration of the respiratory function for a few years after recovery.
In patients with hypercapnic respiratory failure, mortality is increased because these patients have a chronic respiratory disorder and other comorbidities (cardiopulmonary, renal, liver or neurological diseases). These patients may also have poor nutritional status.

In patients with COPD and acute respiratory failure, mortality has decreased in recent years by approximately 26%. Acute exacerbation of COPD causes 30% mortality. The mortality rate for other etiologies has not been well documented.

7. Treatment

The treatment of respiratory failure consists of the following:
I. Prophylactic measures: such as hygiene-dietary rules, prevention of infections through vaccination, immunomodulation, eradication of outbreaks, smoking ban
II. Identification, elimination of disease-worsening causes: infections, treatment errors, sedative medication, uncontrolled oxygen therapy
III. The background treatment

A. Medical: includes the treatment of the underlying disease.
B. Long-term oxygen therapy:
In the case of hypoxemic patients, oxygen therapy improves mental capacity and effort. Prior to administration, the blood gas concentration at rest is determined, and the PaO2-SaO2 correspondence is checked. The need for O2 established at rest will have to be increased during exercise and during sleep with 1L / min. In order to be effective, the use of xigen-therapy is at least 16 hours / day.

Criteria for long-term oxygen therapy:
• PaO2 ≤ 55 mmHg or SaO2 ≤ 88%, with or without hypercapnia;
• PaO2 ≤ 60 mmHg or SaO2 ≤ 90% and signs of pulmonary hypertension, polycythemia (hematocrit> 55%) or heart failure.
C. Assisted ventilation
Noninvasive ventilation(NIV) provides ventilator support during the treatment of reversible conditions, reduces fatigue of the respiratory muscles, corrects hypoxia and hypercapnia.

Table 6. Advantages and disadvantages of noninvasive ventilation

Advantages	Disadvantages
• Reduces mortality, morbidity **• Improves patient comfort (ventilation breaks)** **• Maintains airway protection mechanisms • Can also be used outside the IT service** **• Avoid accidents due to orotracheal intubation**	• The mask may be uncomfortable or allow significant air loss, which may ultimately lead to NIV failure (multiple sizes, mask types). • There is a risk of complications: ulceration, necrosis (especially at the nose), eye irritation, nasal and sinus congestion, sleep fragmentation, secretion retention • The airways are not protected and cannot be aspirated • Requires trained personnel and the possibility of continuous monitoring, (frequent blood gasometry).

NIV indications:

• Respiratory acidosis ($PaCO_2 \geq 45$ mmHg and arterial $pH \leq 7.35$).

• Tahipnea (> 24 breaths / minute)

• Severe dyspnoea with clinical signs suggestive of exhaustion of the respiratory musculature, increased respiratory labor or both, such as the use of the accessory respiratory musculature, paradoxical abdominal movement or narrowing of the intercostal spaces.

• Persistent hypoxemia despite oxygen supplementation.

Contraindications of NIV

Absolute	Relative
• Respiratory arrest **• Impossibility of airway protection (coma, sedation)** **• Airway obstruction** **• Inability to remove secretions** **• Major hemodynamic instability, life-threatening arrhythmias** **• Undrained pneumothorax**	• Fractures / facial burns • Recent surgery on the face, upper airway or digestive tract • Abundant secretions • Intestinal occlusion • Vomiting • Severe comorbidities • Morbid obesity • Extreme anxiety • Severe hypoxemia refractory to oxygen administration (PaO_2 <60mmHg) • Non-compliant, restless patient

Non-invasive ventilation can be performed with CPAP (continuous positive pressure in the airways), VSP (spontaneous pressure ventilation with support) or BiPAP (positive pressure ventilation at two levels).
In the case of therapeutic failure with noninvasive ventilation, the use of invasive mechanical ventilation with orotracheal intubation probe (IOT) is used. Treating these patients requires admission to the intensive care service for more complex monitoring.

Criteria for orotacheal intubation
- Hemodynamic instability, neurological status degradation **- PaO_2 <40mmHg, $PaCO_2$> 90mmHg, pH <7.2**

D. Pulmonary Rehabilitation

E. Psychotherapy, nutritional counseling

F. Surgical (lung volume reduction, lung transplant)

Bibliography:

1. Pneumology course for resident doctors under the editorial Voicu Tudorache, Mirton 2013

2. Murray & Nadel's Textbook of Respiratory Medicine, 6th ed., 2016 Saunders, Elsevier

3. ERS Handbook of Respiratory Medicine 3rd Edition, publisher European Respiratory Society, 2019

4. Interpretation of Pulmonary Function Tests, A Practical Guide, Robert E. Hyatt, Paul D. Scanlon, Masao Nakamura, Third Edition, 2009

5. Harrison's Pulmonary and Critical Care medicine, 2nd edition, Joseph Loscalzo, 2013

6. Egan's Fundamentals of Respiratory Care, Eighth Edition, Robert L ilkins, James K. Stoller, Craig L. Scanlan, 2003

7. Chest medicine, Essentials of pulmonary and critical care medicine, second edition, Ronald B. George, Richard W. Light, Michael A. Matthay, Richard A. Matthay, 1990

8. Guide for the use of non-invasive ventilation in Emergency Units, Teodora Sorana Truta, Cristian Boeriu, Simona Bratu, Emilia Turucz

9.Ali, J., W.R. Summer and M.G. Levitzky (eds.), Pulmonary Pathophysiology, 3rd Ed, McGraw-Hill, New York 296 pp., 2010.

10. http://www.srp.ro/GOLD-Global-Initiative-for-Chronic-Obstructive-Lung-Disease-120.html

5. BRONCHIAL ASTHMA OF ADULT

Overview

Bronchial asthma is a common, chronic, potentially severe disease, often underdiagnosed. Almost always there is a trigger allergen, which may remain unknown. Exacerbation is most often mistaken for over-infection, which leads to an abusive use antibiotics.

Due to under-diagnosis, as well as under-dosage of inhaled cortisone (because of corticophobia), bronchial asthma remains undertreated. The epidemiological evolution of asthma is somewhat paradoxical: the incidence and mortality rate increases, despite an increasingly complex and efficient therapeutic arsenal.

Definition

Asthma represents a chronic inflammatory syndrome of the airways associated with bronchial hyper-reactivity, leading to recurrent episodes of wheezing, dyspnea, chest constriction and coughing, especially at night or in the early morning. Numerous cell types and biochemical mediators participate in the inflammatory process. Functionally, there is a marked obstruction of the airflow, variable and often reversible spontaneously or under treatment.

Epidemiology

It affects around 300 million individuals worldwide. The prevalence of asthma has increased over the past 30 years. Approximately 10-12% of adults are affected globally. Asthma correlates with the increased prevalence of atopy and allergies, constituting a public health problem with a significant economic impact.

Physiopathological mechanism

Due to the interaction between genetic and environmental factors (allergens, viruses, pollution), there is an "immune deviation" in the T-helper1 (Th1) and Th2 cell lines in the bronchi, with the predominance of the Th2 line. The airborne allergen is captured and processed by macrophages / dendritic cells that will send signals to the peribronchial ganglionic system (BALT) where this cell line (Th2) will be activated. The Th2 cell line will synthesize and release IL4 and IL13 that will act on B cells, triggering the inflammatory cascade on the plasmocyte - IgE - mast cell - eosinophil.

The acute / immediate phase of the immune response is triggered by a wave of mediators (histamine, leukotriene, IL4, IL5, and GM-CSF) secreted by mast cell and eosinophilic degranulation. Due to the presence of these cells and mediators of inflammation, in the epithelium and the smooth musculature of the airways an inflammatory infiltrate will be formed, generating vasodilation and peeling, with hyperplastic excitation of the musculature and the bronchial glands.

Bronchial hyperreactivity (HRB) with respect to various stimuli (cold air, allergens, irritants, infectious agents) occurs due to epithelial decompression, which will expose the dendrites of the subepithelial sensory nerves.

Bronchoconstriction is a consequence of HRB that causes the bronchial lumen to decrease. The bronchial lumen is further diminished by the synergistic action of the edema produced by vasodilation and by the intraluminal mucus secretion of the excised bronchial glands. Loss of bronchoconstriction inhibitors (the relaxation factor derived from epithelium, PGE2, and

endopeptidases that metabolize endogenous bronchoconstriction) are the result of epithelial peeling and mucosal edema, which contribute to the onset / maintenance of HRB.
The late phase of the immune response - phase in which the remodeling will be constituted, chronically irreversible process, appears with the activation of the trophic epithelio-mesenchymal unit.), fibroblast proliferation (via EGF), vascular hyperplasia (endothelin 1 and VEGF). The repeated injury of the airways, accompanied by cycles of inflammation and increasingly deficient repair, constitutes the remodeling functionally translated by fixed, irreversible bronchial obstruction. This can be prevented by aggressive and early administration of anti-inflammatory medication.
From the clinical point of view, in the constitution of this disease, there is a lineage consisting of several successive phases: initiation / induction → consolidation → persistence → progression.
In conclusion, the risk factors involved in the development of asthma are:
Predisposing factors: genetic susceptibility (atopy) to developing an IgE-mediated response to common aero-allergens.
Causal factors (which determine the occurrence of the disease in susceptible persons): allergens, professional factors, aspirin drugs and NSAIDs.
Contributing factors / triggers (favor the appearance of the disease in case of exposure to causal factors): viral or bacterial respiratory infections, diet, active / passive smoking, outdoor or indoor air pollution, obesity, environmental factors (cold air, fog), physical effort, emotional factors (anxiety, stress, fatigue).

Pozitive diagnosis
The "classic" clinical characteristics of asthma - less specific, but highly variable over time.
The four cardinal symptoms of asthma are: *coughing, dyspnea, wheezing and chest tightness*. These can occur in different combinations or degrees of intensity. The general feature of these symptoms is variability over time. They are accentuated at night / in the morning or at a sustained physical effort.
The triggers can be: exertion, tracheobronchial tract infections, exposure to specific allergens, air pollutants, cigarette smoke, cold air, high stress, gastro-esophageal reflux, etc.
Dyspnea: described predominantly in expiration, initially occurs paroxysmally. Night and / or exercise manifestations are suggestive; in advanced cases it is installed at the slightest effort.
Cough: initially unproductive, but towards the end of the crisis can be accompanied by difficult mucous expectoration in small quantities. The sputum may be yellow, given the abundance of eosinophil cells grouped or not in the classic Curschmann spirals. It is most often painful, repetitive, sometimes violent, causing chest pain or vomiting. In asthmatic cough, conventional antitussives are ineffective.
Wheezing: it is a characteristic noise of asthma, but also of other obstructive diseases. It is often perceived by the patient and described as whistling, snoring, murmuring. It occurs more frequently during exacerbations and in dorsal or lateral decubitus.
Chest constriction: diffused throughout the thoracic surface, it is described as a feeling of pressure or tightness, which impedes deep inspiration. It is less commonly encountered compared to the other accusations. It seems to be generated by the diffuse and extensive spasm of the bronchi.
Sputum is generally produced in small quantities, but in some patients there may be an increased mucus production, with a typical adherent mucus, which is difficult to expectorate. It has a

gelatinous or pearl-like appearance, containing Curschmann spirals and Leyden crystals, which give a yellowish color.
Because of this, it is often mistaken for a sputum in an infection, and, as such, it is falsely treated with antibiotics.

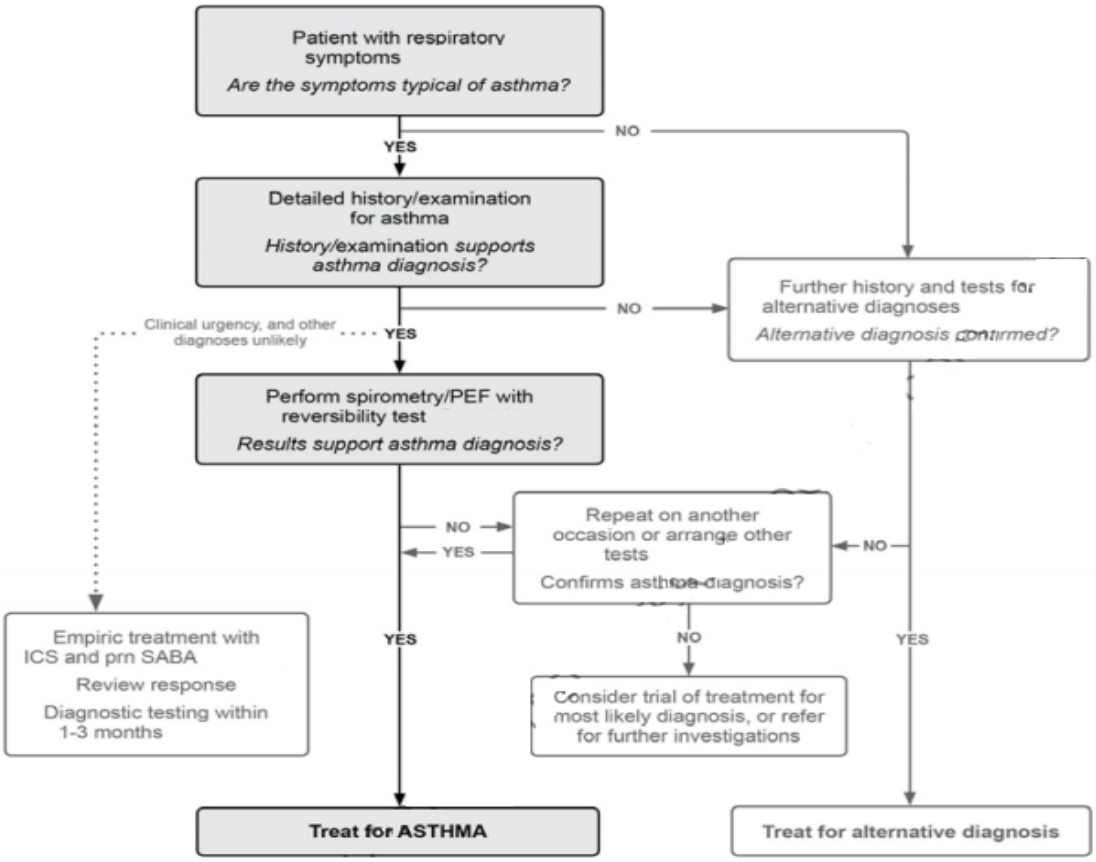


Figure 1. Diagnosis algorithm in asthma (GINA 2018)

Asthma crisis. Under stable conditions of mild asthma, physical examination is usually normal, but becomes characteristic during the onset of the crisis. From the point of view of the temporal pattern, the crisis starts in the second part of the night, the patient being awakened from sleep by a progressive paroxysmal dyspnea, coughing and wheezing (giving him a feeling of intense panic). Because of the need to "have as much oxygen as possible", he gets out of bed and goes to the window to open it. Supported on the window sill, the patient adopts an inclined position that allows him to involuntarily use the accessory respiratory musculature. After a period of 20-30 minutes, if bronchodilatory medication is not given and the crisis is not very severe, the symptomatology is gradually remitted, with the expectation towards the end of the crisis, of a minimal amount of pearl or yellowish sputum. If the physical examination could be performed during a seizure, then the following signs could be objectified: thorax with diminished respiratory enlargement (blocked), prolonged expiration, hypersonality, diminished bladder murmur covered by snoring, wheezing and sub-repetitive pumbar noise (which is specific to asthma), intense anxiety and heavy sweating.
Status asthmaticus, is a particular form and severity of the asthma crisis manifested by intense dyspnea, asphyxia, polypnea, cyanosis, tachycardia, decreased blood pressure and phenomena of

right heart failure. The asthma attack can occur after exposure to specific allergenic antigens, after infections or after exposure to a sudden increase in pollution. The prodroms can precede the bronchial asthma crisis, but not necessarily. The sneezing, tears or rhinorrhea that announce the onset of the crisis represent the aura of the crisis and must be integrated into the asthmatic picture.

The symptomatology model is seasonal, discontinuous and perennial.

Allergic hereditary-collateral history: they are identified based on anamnesis. The most often described atopic diseases are allergic rhinitis, contact dermatitis and even asthma.

Any **factors that maintain or trigger the asthmatic** picture of the asthma patient's habitat will always be carefully analyzed: housing situation: new / old house (with dampness); the presence of carpets or drapes colonized with various mites; pets: cats, dogs, cages; the presence in the garden or around the house of certain intensely allergenic plants such as ambrosia, etc.

Also, the patient must be aware of the multitude of aggravating factors such as: respiratory tract infections, physical exertion, cigarette smoke, drugs (NSAIDs, β-blockers), emotional factors, varnishes / paints, perfumes or thermal differences.

Family assessment: child / couple relationships, degree of tolerance and support provided by family members.

B) Functional respiratory exploration

Spirometry shows a reversible obstructive ventilator syndrome and highlights the reversibility after administration of β2-agonist bronchodilator (FEF1 increase > 12% and absolute value > 200 ml, compared to baseline). The diagnosis can also be confirmed by the specific (with the antigen incriminated) or nonspecific (methacholine) bronchoconstriction assay with FEV1 drop > 12% or more than 200 ml.

Peak-flow metrics (PEF): It is recommended for patients with clinical suspicion of asthma and with normal spirometric values. A daily variation of 20% makes the diagnosis of asthma. Monitoring for 2-4 weeks at home, can detect the variability of the airflow limitation and indicate the severity of the evolution depending on the type of chart offered: slow slide progress, chaotic path (uncontrolled asthma, non-compliant asthma), circadian variations of more than 30-40% of the basal value with "morning dipper" in severe asthma. It should be noted that lowering PEF can prevent for hours or even days the symptoms of an asthma attack.

Testing the reversibility to cortisone - only in untreated asthma or with the presumed imminence of irreversible chronic course.

Bronchial Challenge Test: Decreased FEV1 by ≥ 12% or ≥ 200 mL from the predicted value after physical exertion certifies asthma diagnosis.

C) Allergic testing: - *Skin tests (prick-test)* are performed by applying a few drops of the solution of allergenic extract on the front of the forearm. The allergens will penetrate the skin without bleeding. In case of a positive reaction, a papule surrounded by erythema appears at the place of application.

- *Serological tests: fadiatop or ImmunoCAP:* Fadiatop contains only inhalation allergens and is aimed at patients with respiratory tract symptoms. It is a test that differentiates atopic diseases from non-atopic diseases. It uses a mixture of representative allergens to highlight specific IgE antibodies in the patient's serum.

- *Inhalation testing, with the substance presumed to be incriminated or Methacoline:* practiced in patients with asthma symptoms, but with normal lung function tests in repeated determinations.

D) Laboratory: - *Blood eosinophilia (> 400 / mmc) + sputum eosinophilia / nasal secretions;*
- *Basophil degranulation test; The histamine release test.* Detects allergen-specific IgE related to cells, as well as direct degranulation through non-IgE mechanisms;
- *NO in exhaled air (FeNO):* increased levels of NO correlate with eosinophil-based inflammation of the airways even in an asymptomatic patient or in those with poor symptomatology;
- *Blood ECP (cationic protein of eosinophils)* is useful in monitoring inflammatory disorders and represents a better marker than IgE in the allergic inflammatory process;

E) Arterial gasometry is especially important in moderate-severe exacerbations that do not respond to treatment, in which the clinical status suggests a rapid evolution towards a very severe form (status astmaticus), with the onset of acidosis (PaO2 decreases strongly and the PaCO2 increases), which may involve intubation and mechanical ventilation.

F) Chest X-ray: In mild to moderate forms, the classical radiological examination offers normal aspects. In severe forms, the distension of the thoracic box is detected and opacities appear in the aspergillary asthma. Radiological examination may be useful in the detection of penumothorax (complication of exacerbation) or pneumonic processes due to infection. In the crisis, segmental or sub-segmental infiltrates and atelectasis due to mucus plugs can be observed.

The severity step of the asthma and the therapeutic scheme is established on the basis of clinical components (symptoms, moment of their occurrence, limitation of physical activities, number of exacerbations), frequency of use of rescue medication and severity of airway obstruction.

Differential diagnosis
Wheezing can be generated by other entities, not just asthma. The axiom "not all that whistles is asthma" remains valid. The following table lists the types of wheezing and the pathology that may cause them.

Table 1. Differential diagnosis of wheezing

PULMONARY		**EXTRA-PULMONARY**
Monofinoc wheezing	**Polifonic wheezing**	**Polifonic wheezing**
Endobronchial tumor/granuloma Stenosis/tracheal/bronchial compression (tumors, cysts, hematoms) Retrosternal Timom Foregin body inhalled Intrabronchial anomaly Scar Stridulous laryngitis	COPD **Asthma** Bronchiolitis Tracheo-bronchial diskinesia	Cardiac asthma Anaphylactic shock Carcinoid syndrome Allergic angina Gastro-esophagus reflux

The differential diagnosis is made with the entities that cause: **- dyspnea:** COPD, coronary artery disease, congestive heart failure, pulmonary embolism, gastroesophageal reflux disease; **- cough:** sinusitis, rhinitis, chronic or postviral bronchitis, otitis, bronchiectasis, cystic fibrosis,

pneumonia, diffuse interstitial fibrosis; **- diseases that cause airway obstruction:** chronic bronchitis and emphysema, obliterative bronchiolitis, cystic fibrosis, laryngeal impairment, extrinsic or intrinsic trachea.
The most common confusion is between COPD and ASTHMA. Both are obstructive diseases that are based on airway inflammation, but which have different characteristics. However, with advancing ages, there is a cumulative comorbidity and pathophysiological entanglement leading to what is called the "overlap syndrome". The entities that generate the overlap syndrome, and which are the most important in frequency and difficulty to treat, are COPD and heart disease. This syndrome will be described in detail in the COPD chapter.

Evolution and prognosis
Asthma is a disease with undulating and unpredictable evolution, with exacerbations due to the exposure to various pneumo-allergens, the superposition of a respiratory tract infection, the interruption of the treatment or the overdose of the medication.
The onset of the crisis may be sudden (minutes-hours) or slowly progressive over many days (exacerbation). The evolution of an exacerbation goes through several phases, each requiring adjustment to the increased degree of therapy. Parameters and degree of intensity are described in table 2.

Table 2. Clinical-functional decline during asthma exacerbation

Parameters	Easy	Moderate	Severe	Respiratory stop imminence
Dyspnea	Walking	Speaking	At rest, the patient is bent over	Bradypnea
Respiratory Frequency	High	High	Superficial polypnee(>30/min)	
Use of accessory muscles (suprasternal depression)	Usually not	Usually yes	Usually yes	Paradoxical thoraco-abdominal movements
Wheezing	Moderate	Accentuated	Usually accentuat	Absent!!
Behavior	It can be uneasy	Usually uneasy	Frequently uneasy	Confused, drowsy (hypercapnic encephalopathy)
Speech	Use of phrases	Sentences	Words	No speech
Cardiac frequency	<100	100-120	>120	Bradycardic
Paradoxical pulse	Absent <10mmHg	May be present 10-25mmHg	Frequently present >25mmHg	Absence indicates severe fatigue of the respiratory muscles
PaO2 PaCO2 PH	Normal <45mmHg Normal	>60mmHg <45mmHg N	40-60mmHg >45mmHg,cyanosis N	<40mmHg >44mmHg Acydosis
PEF After beta2 agonist	>80%	60-80%	<60% <100l/min	Dose not cooperate
TA EKG	N N	N N	Low TC, signs of CPC	Imminence of colaps, ventricular tachyarrhtymias

The absence of clinical manifestations and paraclinical changes signifies the notion of control. Thus, asthma can be considered as balanced by treatment, according to the following table. However, the level of control must also be reported at the therapeutic stage in which the patient is enrolled.

Table 3. The level of control of Asthma

Characteristics	**Controlled (all of the following)**	**Partial controlled (Any of the following in any week)**	**Uncontroled**
Daytime symptoms	**2 or less / week**	**>2 / week**	**At least 3 features present in any week**
Limiting activity	**Without**	**Present**	
Night time symptoms / awakenings	**Without**	**Present**	
Rescue medicamentation/ "reliever"	**or less/ week**	**>2 times / week**	
Pulmonary function (PEF or FEV1)	**Normal**	**< 80% of predicted best personal value (if known) on any day**	
Exacerbation	**Without**	**≥1 /year**	**1 / week**
Valide questionnaires			
ATAQ*	**0**	**1-2**	**3-4**
ACQ**	**≤ 0.75**	**≥ 1.5**	**N/A**
ACT ***	**≥ 20**	**16-19**	**≤ 15**

*** asthma therapy assessment questionnaire. **asthma control questionnaire. *** asthma control test**

In the case of *uncontrolled asthma*, the causes that may impede the control will be analyzed: the patient's knowledge about his disease and the self-management of the disease, compliance (following the treatment and inhalation technique), smoking, exposure to allergens, other asthma-related diseases (allergic rhinitis, BRGE, SAS), drug intolerances (aspirin, NSAID, b-blocker or IECA), chronic infections, psychological factors or the existence of systemic comorbidities are possible causes that may interfere with adequate control.

If the patient is properly treated and compliant, the prognosis is favorable. After more than 10 years of disease evolution, due to the refractory bronchial remodeling, 2-8% of patients develop irreversible bronchoconstriction. Phenotypes of unstable asthma ("brittle asthma" or fragile asthma) may have a more reserved prognosis. Factors that increase the risk of death by asthma will be listed in order of severity: history of hospitalization in the Intensive Care Unit, intubation, hospitalizations or emergency consultations in the last year, abuse of inhalation bronchodilators, comorbidities (cardiovascular diseases, psychiatric disorders), social status -economic precarious (lack of access to medical care) or allergy to *Alternaria*.

Treatment

The long-term goals in asthma management are:

a) Prevention of symptoms and the chronic course of the disease;
b) Maintenance of normal lung function;
c) Maintaining an activity within normal limits (including tolerance to physical effort);
d) Prevention of exacerbations and hospitalizations;
e) Avoidance of adverse effects of medicines.

Principles of anti-asthmatic treatment:

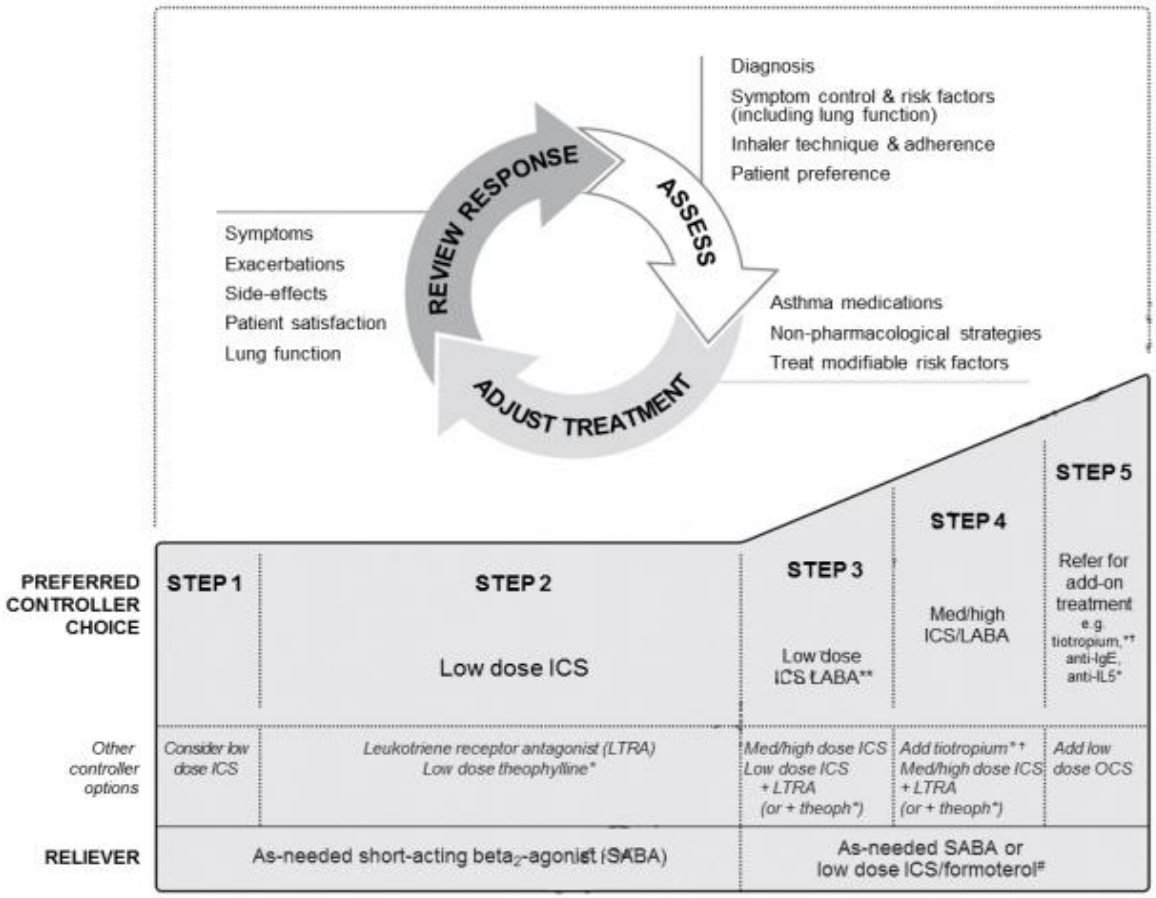
- Evacuation of the allergen;
- Removal of triggers / aggravating factors;
- GINA (Global Initiative for Asthma) chronic treatment;
- Treatment of acute phases: crisis, exacerbation;
- Immunotherapy

Long-term chronic anti-inflammatory treatment is mandatory, with asthma being a chronic disease developed on the basis of a chortico-sensitive inflammatory model. The treatment can be doubled at the time of exacerbation, by a broncho-dilatory "rescue" medication. The recommendation of anti-inflammatory (long-term) maintenance medication from the earliest stages of the disease is based on bronchial biopsies performed in both newly diagnosed and chronic asthmatics. In both situations there is a similar degree of airway inflammation and sub-epithelial fibrosis. Even more, airway remodeling can be evidenced from the early stages before the symptoms manifest themselves clinically.

For effective treatment, the education of the patient is a fundamental component. The knowledge of the administration of the medication and of the inhalation technique, the determinism of the disease, the prevention or recognition of exacerbations, the importance of the complications, as well as the delivery of an action plan are part of the patient's education. The claim *"chronic obstructive respiratory disease management is 10% medication and 90% education"* has already become an axiom.

Once anti-asthmatic treatment has been initiated, subsequent decisions are based on a cycle of evaluation, treatment adjustment and analysis of response to therapy. In order to achieve good results, treatment should be initiated as soon as possible after the diagnosis of asthma has been established.

Figure 2 shows the step therapy with the recommendation of step up or step down of the medication, depending on the evaluation cycles. Even if symptom control (including lung function) is achieved, dose reduction is not recommended to occur earlier than 3 months, because the result should be strengthened - inflammation is not fully controlled in short intervals by the rapid, upward, "waltz" of the anti-inflammatory drug.



* Existing data only for budesonide / formoterol. # Addition of SLIT therapy for patients with allergic rhinitis and FEV1> 70% of predicted.
† Administered separately or in combination. ‡ Low dose of CIS / formoterol is the rescue medication for patients who have been given low doses of budesonide / formoterol or low doses of beclomethasone / formoterol for background treatment and rescue.

Figure 2. Drug therapy according to the level of control (GINA 2019)

Anti-asthmatic medication is divided into two main categories:

1) Chronic long-term (control) anti-inflammatory treatment in decreasing order of efficiency (glucocorticoids - leukotriene inhibitors - mast cell stabilizing agents)

2) Treatment of rapid improvement (rescue - "reliever") that inhibits the contraction of smooth bronchial muscles (β2-agonists, anticholinergics and methylxanthines)

1. Chronic long-term anti-inflammatory treatment:

Corticosteroids: --inhalers*: beclomethasone, budesonide, flunisolid, fluticasone, mometasone, etc.

--systemic: prednisone, methylprednisolone, betamethasone, etc

Corticosteroids are the anti-inflammatory drugs of choice both during periods of calmness and exacerbations, reducing the activation of inflammatory cells (T lymphocytes, eosinophil cells, mast cells), as well as their number in the airway mucosa.

Treatment initiated early in low doses of ICS leads to improved lung function, as opposed to starting treatment several years after the onset of symptomatology. ICS are indicated at low doses regularly to all patients that present: asthma symptoms more often than twice a month, waking up due to asthma more than once a month, or any asthmatic symptom plus any risk factor

for exacerbations (FEV1 low, OCS in the last 12 months, hospitalization in the Intensive Care Unit for asthma). ICS reduce bronchial hyperactivity, prevent the onset of symptoms, decrease the number of exacerbations and the need for OCS, increasing the quality of life. The most common side effects of ICS administration are oro-pharyngeal candidiasis and dysphonia.
Systemic CSs are indicated in therapeutic step 5 when asthma cannot be controlled with high doses of ICS during exacerbation and asthma conditions. The OCS effect is installed slowly after 3-6 hours after administration. It is recommended to use short cures of 5-7 days with low doses of Prednison 1mg / kg / day up to 50mg. No progressive dose reduction is necessary if treatment has been given for less than 2 weeks.

Antileukotriens

Leukotrienic receptor antagonists: Montelukast
Inhibitors of leukotriene synthesis: Ziluton
Leukotrien antagonists are given orally in single doses, preferably in combination with ICS. They have lower broncho-dilatory and anti-inflammatory effects than ICS / LABA and are indicated for the control of the nocturnal symptoms and in the stress induced asthma.

c) Chromones (very rarely used): Nedocromil, Chromoglycated
There are control drugs in asthma, which inhibit mast cell degranulation and activation of the sensitive nerves, thus being effective in blocking stress-induced asthma and allergens.

2. "Rescue" medication - with rapid symptom relief. It is divided into the following classes:

β2 - agonists

β2 - short-term agonists (SABA): salbutamol, terbutaline, etc.
They have a rapid effect, in 5-10 minutes. They are used in the bronchospasm attack. Excessive use means a lack of control of the disease and the need to introduce or increase anti-inflammatory treatment.
β2 - long-acting agonists (LABA): salmeterol, phenoterol, etc.
It is installed slowly, in 15-30 minutes and the effect lasts ≥ 12 hours. If average doses of ICS fail to gain control, adding LABA to ICS improves symptoms, pulmonary function, and lowers the number of exacerbations, a lot better than doubling the ICS doses.

Anticholinergics

Short-acting anticholinergics (SAMA): ipratropium.
Long-acting anticholinergics (LAMA): tiotropium.
They settle slowly and have a lower broncho-dilatory effect. They are indicated in patients with coexisting cardiac comorbidities and in whom β2-mimetics and methylxanthine may be dangerous. They can be used as an adjuvant option in therapeutic step 4 or 5 for adult patients with a history of exacerbations despite treatment with ICS + LABA.

β2 combinations - short-term agonists + short-acting anticholinergics in a single inhaler: ipratopium + terbutaline

Methylxantine: theophylline.
Although, methylxantines have been prescribed for over 70 years in bronchial asthma, they are rarely used anymore due to their limited broncho-dilatory effect and frequent side effects (headache, insomnia, agitation, nausea, vomiting, anorexia or arrhythmias which can be fatal). Although in the current format of the "GINA 2019" guide theophylline has lost its initial position in the treatment of asthma, due to the low costs or the patient's preference, theophylline remains a solution. These can be administered as other options in the treatment of the substance, either in combination with the CIS in the therapeutic stages 3-4.

Anti-IgE antibodies (Omalizumab) is a blocking antibody that neutralizes circulating IgE, not cell-bound IgE, thus inhibiting IgE-mediated reactions by blocking the inflammatory cascade at multiple levels. Treatment reduces the number of exacerbations in patients with severe asthma and may improve control of asthma. However, because the treatment is very expensive, it will be indicated in step 5 for patients who are not controlled with maximum doses of CIS and have circulating IgE values > 76 IU / ml. Omalizumab is given in subcutaneous injections every 2-4 weeks, with insignificant side effects.

For step 5, in the case of asthma with increased eosinophilia that does not respond to omalizumab, antibodies against IL5 (mepolizumab, reslizumab) or anti IL5 receptor (benralizumab) may be used.

Immunotherapy (hyposensitization). It has not been shown to be very effective in controlling asthma and it can cause anaphylaxis. Its place and role will be estimated after calculating the following aspects: 50% of the cases selected for immunotherapy do not find a real benefit; the beneficial effect is "erased" after about 1 year of immunotherapy, even to those who initially responded well; the allergen must be precisely identified; there should be no polysensitization; age of administration: child / young adult; accurate dosing / purifications can be performed; there should be no diseases that contravene adrenaline.

The purpose of the chronic treatment is to reach a control of the symptoms, with a pulmonary function appropriate to the age and with the minimum possible medication. The guide "GINA 2019" has a progressive approach, in stages, with the adjustment of the treatment to promote a state of health that defines the notion of controlled asthma. Therefore:

STEP 1: *Preferred option:* as-needed inhaled short-acting beta-2 agonist (SABA). They are highly effective for the quick relief of asthma symptoms. *Other options:* Regular low dose ICS should be considered.

STEP 2: *Preferred option:* regular low dose ICS + as-need SABA. Treatment with ICS at low doses reduces asthma symptoms, increases lung function, improves the aquality of life and reduces the risk of exacerbation

STEP 3: One or two controllers + as-needed reliever medication. *Preferred option:* combination low dose ICS/LABA as maintenance treatment + as-needed SABA or combination low dose ICS/formoterol (budesonide or beclometasone) as both maintenance and reliever treatment.

STEP 4: Two or more controllers + as-needed reliever medication. *Preferred option:* combination low dose ICS/formoterol as maintenance and reliever treatment or combination medium dose ICS/LABA + as-needed SABA. *Other options:* Tiotropium (long acting-muscarinic antagonist) by mist inhaler may be used as add-on therapy for patients with history of exacerbations

STEP 5: Higher level care/and **add-on treatment**. *Treatment options include:*

Add-on Tiotropium;

Add-on anti-immunoglobulin E (anti-IgE) (Omalizumab) for patient with moderate or severe allergic asthma that is uncontrolled on STEP 4.

Add-on anti-interleukon-5 treatment (mepolizumab) for patient with severe eosinophilic asthma that is uncontrolled on STEP 4.

Sputum guided treatment for patients with persisting symptoms or exacerbation despite high dose ICS or ICS/LABA. Treatment may be adjusted based on sputum eosinophilia (>3%).

Add-on low dose oral corticosteroids may be effective for some adults with severe asthma and poor symptom control or frequent exacerbation despite good inhaler technique and adherence with STEP 4 treatment.

The treatment of various asthmatic phenotypes (severely fragile asthma, premenstrual, professional asthma, etc.) requires special elaborated approaches and treatments, which exceed our intention not to address specialists, but only to familiarize students with common asthma, encountered in 80% of cases.

Non-pharmacological interventions

In order to contribute to symptom control and risk reduction, in addition to medication, other therapies and strategies must be considered:

• *Smoking Cessation Counseling:* At each visit, smokers will be encouraged to quit smoking. The electronic cigarette cannot be considered a substitute for the classical one, because it has more prominent respiratory and inflammatory mechanical effects in patients with asthma than the classic cigarettes. They cause the faster decline of lung functions, increase the frequency of exacerbations and reduce asthma control.

• *Physical exercises:* patients with asthma will be encouraged to practice constant physical activity. Advice will be given on the management of stress-induced bronchoconstriction.

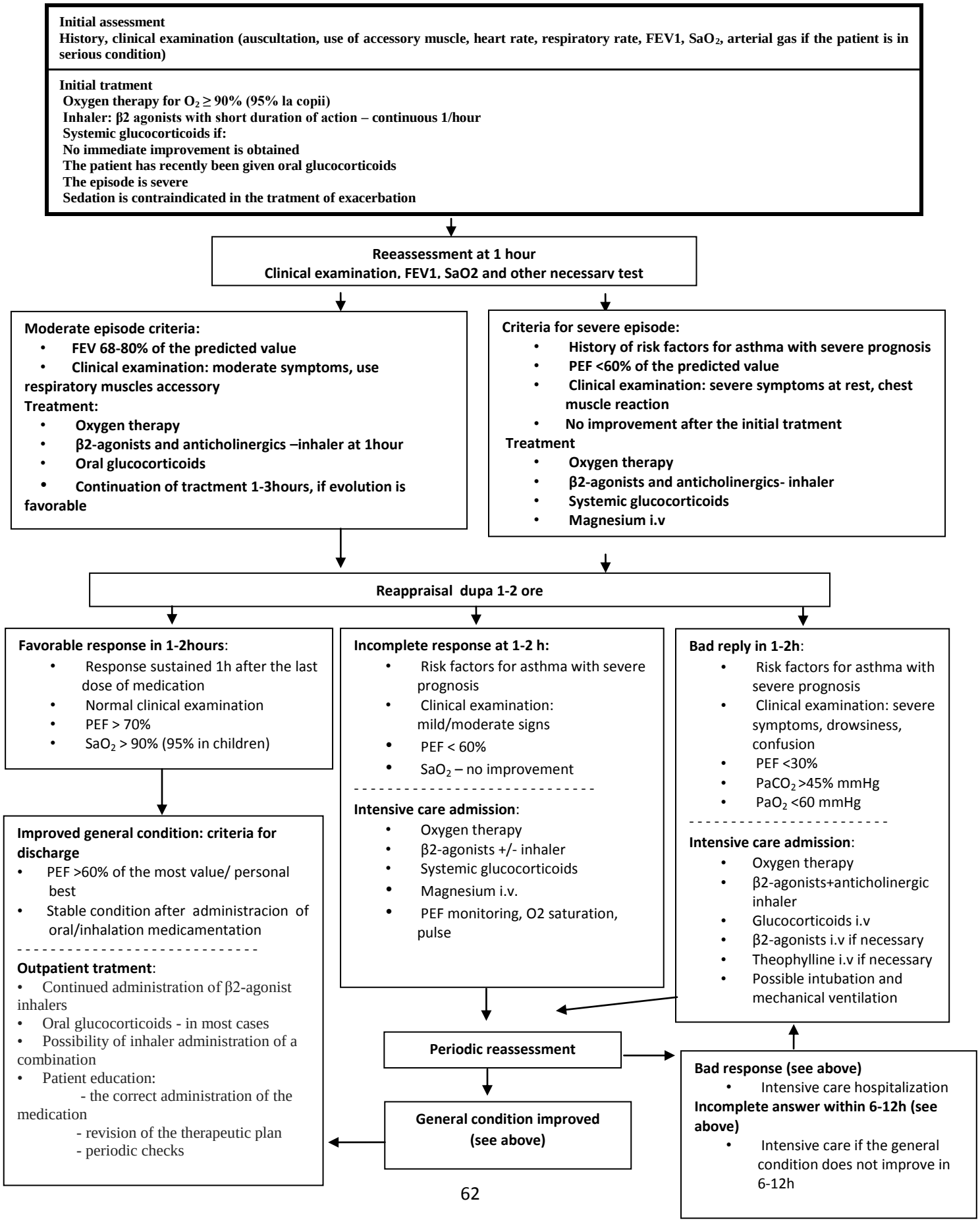
• *Professional asthma*: All patients with asthma onset in adulthood will be asked about professional conditions, with the identification and elimination of allergen sensitizing factors in the professional environment as soon as possible. For this purpose PEF-metrics at home will be used compared to its values at the workplace.

• *Medications:* caution in the administration of NSAIDs / aspirin, non-selective beta blockers, conversion enzyme inhibitors (ACEI), cholinergic agents (eg glaucoma), etc.

Monitoring

The patent will have medical visits periodically, usually every 3 months, or whenever the situation requires (exacerbation). The control of symptoms (according to the established table - Table 3) and risk factors, inhalation technique and adherence will be evaluated. On the occasion of the each control visit, the doctor will investigate whether or not there are post-drug side effects (dysphonia - inhaled post-corticosteroid; tremor, tachycardia, agitation - post-bronchodilatory medication).

Treatment in asthma crisis (in figure 3)


Initial assessment
History, clinical examination (auscultation, use of accessory muscle, heart rate, respiratory rate, FEV1, SaO2, arterial gas if the patient is in serious condition)
Initial tratment
Oxygen therapy for O2 ≥ 90% (95% la copii)
Inhaler: β2 agonists with short duration of action – continuous 1/hour
Systemic glucocorticoids if:
No immediate improvement is obtained
The patient has recently been given oral glucocorticoids
The episode is severe
Sedation is contraindicated in the tratment of exacerbation
Reeassessment at 1 hour
Clinical examination, FEV1, SaO2 and other necessary test
Moderate episode criteria:
FEV 68-80% of the predicted value
Clinical examination: moderate symptoms, use respiratory muscles accessory
Treatment:
Oxygen therapy
β2-agonists and anticholinergics –inhaler at 1hour
Oral glucocorticoids
Continuation of tractment 1-3hours, if evolution is favorable
Criteria for severe episode:
History of risk factors for asthma with severe prognosis
PEF <60% of the predicted value
Clinical examination: severe symptoms at rest, chest muscle reaction
No improvement after the initial tratment
Treatment
Oxygen therapy
β2-agonists and anticholinergics- inhaler
Systemic glucocorticoids
Magnesium i.v
Reappraisal dupa 1-2 ore
Favorable response in 1-2hours:
Response sustained 1h after the last dose of medication
Normal clinical examination
PEF > 70%
SaO2 > 90% (95% in children)
Incomplete response at 1-2 h:
Risk factors for asthma with severe prognosis
Clinical examination: mild/moderate signs
PEF < 60%
SaO2 – no improvement
Intensive care admission:
Oxygen therapy
β2-agonists +/- inhaler
Systemic glucocorticoids
Magnesium i.v.
PEF monitoring, O2 saturation, pulse
Bad reply in 1-2h:
Risk factors for asthma with severe prognosis
Clinical examination: severe symptoms, drowsiness, confusion
PEF <30%
PaCO2 >45% mmHg
PaO2 <60 mmHg
Intensive care admission:
Oxygen therapy
β2-agonists+anticholinergic inhaler
Glucocorticoids i.v
β2-agonists i.v if necessary
Theophylline i.v if necessary
Possible intubation and mechanical ventilation
Improved general condition: criteria for discharge
PEF >60% of the most value/ personal best
Stable condition after administracion of oral/inhalation medicamentation
Outpatient tratment:
Continued administration of β2-agonist inhalers
Oral glucocorticoids - in most cases
Possibility of inhaler administration of a combination
Patient education:
- the correct administration of the medication
- revision of the therapeutic plan
- periodic checks
Periodic reassessment
General condition improved (see above)
Bad response (see above)
Intensive care hospitalization
Incomplete answer within 6-12h (see above)
Intensive care if the general condition does not improve in 6-12h

References:

1. Pneumology course for resident doctors under the editorial Voicu Tudorache, Mirton 2013
2. ERS Handbook of Respiratory Medicine 2nd Edition, publisher European Respiratory Society, 2013.
3. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2019 available at http://www.ginasthma.org/Guidelines/guidelines-resources.html
4. Bronchial asthma: controversies, dilemmas, solutions. Voicu Tudorache, Mirton Publishing, 1997
5. http://www.ukmi.nhs.uk/NewMaterial/html/docs/OmalizumabNMP0601.pdf
6. Internal Medicine Vol I, Viorel Şerban, Excelsior Publishing House, 1995
7. Medical Semeiology, Dan Georgescu, National Publishing House, 2008
8. Is bronchial hyperresponsiveness more frequent in women than in men? A population-based study. Leynaert B, Bousquet J, Henry C, Liard R, Neukirch F. AJRCCM 1997; 156 (5): 1413-20. 9. Harrison Pneumology and Intensive Care, Second Edition, Joseph Loscalzo, ALL 2017 Publishing 9. Wenzel S. Severe asthma in adults. Am J Respir Crit Care Med 2005; 172 (2): 149-60
10. Heaney LG, Robinson DS. Severe asthma treatment: need for characterizing patients. Lancet 2005; 365 (9463): 974-6.
11. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis and management. J Allergy Clin Immunol. 2003; 111 (5): 913-21
12. Banks DE, Wang ML. Occupational asthma: "the big picture". Occup Med. 2000; 15 (2): 335-58.
13. Global Atlas of Asthma - European Academy of Allergy and Clinical Immunology 2013

6. CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC COR PULMONALE

Introduction

In the first part of this chapter we will approach the topic of chronic obstructive bronchopneumopathy (COPD), and later, the chronic cor pulmonale (CP) will be discussed as a complication of chronic obstructive disease.

Chronic obstructive pulmonary disease (COPD) is a treatable and preventable disease. It has become the third leading cause of mortality worldwide. This disease is based on a certain pattern of inflammation that goes far beyond the respiratory tract and, together with other factors, such as smoking, sedentary lifestyle and chronic hypoxemia, is accompanied by major systemic consequences.

Definition

COPD is a multifactorial disorder characterized by chronic airway obstruction, incomplete reversibility, progressiveness and an abnormal inflammatory response of the lung to harmful particles and / or gases. Exacerbations and comorbidities are crucial to the severity and prognosis of the disease. It occurs especially in large smokers who do not have asthma, obliterative bronchiolitis or bronchiectasis.

Epidemiology

In Europe, 44 million patients are diagnosed with COPD. In Romania there are 60 deaths per 100,000 inhabitants. COPD mainly affects people over the age of 40. A large percentage of patients suffering from COPD, as in the case of asthma, remain undiagnosed in the early stages, because the charges of the patients are minor and wrongly attributed to other factors.

Proven risk factors for COPD:

Genetics: alpha1-antitrypsin deficiency, genetic polymorphisms involved in oxidative metabolism and protease-antiprotein balance, atopy, high IgE level, bronchial hyperreactivity.

Exposure to air pollution and particles: (a) cigarette smoke, (b) indoor air pollution (common) with exposure to smoke from cooking or heating with fossil fuels in rooms, (c) outdoor air pollution: organic powders and inorganic, extrafine particles (PM 2.5 / 10).

Other factors: impaired lung growth and development (exposure to cigarette smoke during pre / postnatal period increases the risk of developing COPD); passive smoking; repeated bronchitis and pneumonia before the age of 2 years is associated with a low FEV1.

Clinical aspects

The symptomatology appears especially in heavy smokers (> 20 PY; the number of Packs-Year smoked: it is calculated by multiplying the number of packs smoked per day by the number of years of smoking).

The symptoms are more intense at night and in the morning: coughing with expectoration; dyspnoea; wheezing (not always noticeable); chest pain (causes: a. "right anguish", given by increased pressure in the pulmonary artery; b. ischemic etiology; c. gastro-oesophageal reflux);

Coughing and expectoration: constantly, mainly in the morning upon awakening. It is a chronic cough, with exacerbations in the cold season. The sputum is mucous, in medium quantity, purulent in exacerbations; an increased and purulent volume suggests (in advanced stages) the configuration of bronchiectasis.

Dyspnoea: It has an insidious onset. It has less variability than the one found in asthmatics. It is persistent and progressive, not in line with the degree of functional decline of FEV1. Initially, it is perceived as related to physical exertion (FEV1 < 50% - 70%). It becomes orthopnea in advanced stages. Dyspnea intensifies in exacerbations and exertion. It is quantified by 2 scales mMRC (0-5) and BORG (0-10) where the higher gradations correspond to a more pronounced dyspnea;

Physical signs: appear gradually, with the reduction of FEV1 below 50%. In the early stages, patients may have a completely normal physical examination. The signs are non-specific, consisting of:

- Signs of hyperinflation of the type "chest in barrel": increasing the diameters of the chest, horizontalization of the ribs, narrowing the distance between the sternal fork and the cricoid cartilage (<3 cm), with flattening of the diaphragm. Hypersensitivity to percussion due to emphysema can pe present.
- Prolonged expiration (sometimes > 5 seconds) through the lips (prevents the expiratory collaboration of the small bronchi, by increasing the expiratory pressure);
- Cyanosis (reflecting hypoxemia, polycythemia);
- Use of accessory respiratory musculature;
- The 2nd Cardiac Noise is accentuated, but often its perception is camouflaged by the hyperinflation; the hypertrophy of the right ventricle (the Harzer sign);
- Dilation of the jugular, hepatomegaly and edema in the lower limbs, as well as the signs of hypercapnia (obnubility, headache, flapping tremor), announces the irreversible decompensation of the right heart with the installation of the cor pulmonale (CP).

The presence of digital hippocracy is not characteristic of COPD, thus, it is compulsory to quickly evaluate other possible etiologies, especially of neoplastic nature.

There is a wide spectrum of clinical phenotypes (over 40), of which pink puffer and blue bloaters represent the two extremes with more or less important clinical, functional, imaging and biological characteristics.

Pink Puffers **have dyspnoea, but do not show cyanosis.** They have an increase in alveolar ventilation, PaO2 being almost normal and PaCo2 normal / low. This phenotype evolves into type I respiratory failure. ***Blue Bloaters*** **do not present dyspnoea, but show intense cyanosis.** They have low alveolar ventilation, PaO2 being low and PaCO2 increased. This phenotype evolves towards CP. Respiratory centers in *Blue bloaters* are non-responsive to increased CO2, breathing remaining dependent on the hypoxic stimulus to maintain respiratory effort. Therefore, the administration of O2 should be done with care.

The most common comorbidities and systemic effects associated with COPD are:

- Vascular pathology: - Pulmonary hypertension, right heart failure➡Cor Pulmonale;
- Vascular disease: coronary, cerebral, peripheral arteriopathy;
- Hypertension;
- Musculoskeletal disorders: muscle fatigue, cortisone myopathy, osteoporosis;
- Psychiatric disorders: anxiety / depression, cognitive decline (due to chronic hypoxemia);
- Neoplasms, especially on the aero-digestive tract (lung, mouth, larynx, esophagus)

- Obstructive sleep apnea syndrome;
- Metabolic syndrome and Type 2 Diabetes, in the case of obese patients;
- Nutritional dysfunctions: about 30% of patients have weight loss;
- Sexual dysfunction: decreased libido, impotence.

The severity classification is done by (Figure 3):
a) The classic functional criterion: the value of **FEV1**
b) Symptomatic score**: dyspnea** on the mMRC scale or CAT score
c) Future risk, deduced from the **frequency of exacerbations**

mMRC (Modified Medical Research Council): Grade 0: dyspnoea on intense physical exertion. Grade 1: dyspnea on fast walking. Grade 2: walking slower than people of the same age due to dyspnoea or need to stop when climbing a floor. Grade 3: obliged to stop at less than 100m walking at your own pace. Grade 4: dyspnoea too intense to be able to leave the house, or when performing routine activities such as washing or dressing.
CAT (COPD assessment test) is a questionnaire containing 8 questions covering different areas of the COPD clinical aspects such as: symptomatology, mental status, functional status, fatigue degree, activity limitation degree, imminent exacerbations, etc.
A score of 10 assures us of a good, incipient situation; the interval between 10-20 is the range of moderate forms, and> 20 points to severe forms.

Pathophysiology
The pathophysiological mechanisms create a framework in which the **inflammatory phenomena, the imbalance of the protease-antiprotein balance and of the oxidizing anti-oxidant balance** interfere complexly.
The emphysema and chronic bronchitis are the main factors in the constitution of COPD, altering the pulmonary territory in different degrees and unevenly. The emphysema is defined morpho-pathologically, by the permanent distension of the distal air spaces, with the destruction of the pulmonary acin and without reactive fibrosis. Chronic bronchitis is initially described as a clinical entity, defined by daily productive cough, with a duration of at least 3 months, at least 2 years in a row (in the absence of other entities capable of offering a similar symptomatology - bronchiectasis, cystic fibrosis, etc.). Through the destruction of the alveolar bed, the chronic inflammation, the edema, the hypersecretion of the mucus and the fibrosis, the peripheral airways, but also the central ones are altered. Parenchyma and pulmonary vasculature are also affected.
From a functional point of view, the pathological process can be described chronologically as follows: the limitation of the canalicular airflow determines the appearance of hyperinflation (by increasing the volume of residual- "captive" air) with the alteration of the gas exchanges at the alveolar level, and these changes lead, finally, at the onset of heart disease.
Beginning with the lungs, but becoming systemic in evolution, COPD will be accompanied by skeletal muscle dysfunction (present in up to 40% in severely ill patients), which will affect exercise tolerance and increase cardio-vascular risk as well as cachexia, osteoporosis, etc.
Functional explorations:
Spirometry and flow-volume curve certify obstructive ventilatory dysfunction after inhaling bronchodilator with β2-agonists. Thus, if FEV1 < 80% (sometimes with normal values in the early stages) and FEV1 / FVC < 0.7 of the predicted value and negative bronchodilator test

(FEV1 improvement less than 12% of the theoretical value or less than 200 ml) ± signs of hyperinflation, COPD can be certified.

The diffusion of carbon monoxide (diffused long CO - DLCO) appreciates the degree of emphysematous impairment. Usually, the values are low in COPD (<80%), but they can be normal.

The 6 minute walking test (6 minutes walking test-6MWT) measures the distance traveled by the patient in 6 minutes. At the beginning and at the end of the test a few perimeters are evaluated: SaO2, FC and dyspnea is evaluated according to the Borg scale.

Laboratory

Blood gases are useful in cases of severe COPD, when PaO2 + PaCO2 determinations indicate different degrees of decrease. The compensatory metabolic response to chronic hypercapnia is increased venous bicarbonate.

Polycythemia occurs in the context of chronic hypoxemia and may be an indicator of the need for long-term oxygen therapy (OLD).

Blood eosinophilia is a serum marker of exacerbation risk in patients with a history of exacerbations and may predict the effects of inhaled corticosteroid therapy.

EKG: signs of right atrial and ventricular hypertrophy (➧ Cor Pulmonale).

Radiology - thoracic imaging

Standard / conventional radiography is not a sensitive investigation for the diagnosis of COPD in its early stages. However, its usefulness is demonstrated in differential diagnosis. The x-ray gives the following data: a) initial stages: normal appearance; b) advanced stages: hyperinflation; reducing vascular drawing in peripheral territories; lowering (flattening) of the diaphragm; increasing the projection of the heart and the cardiac area; enlargement of the retrosternal space; increased pulmonary artery diameter (Figure 1).

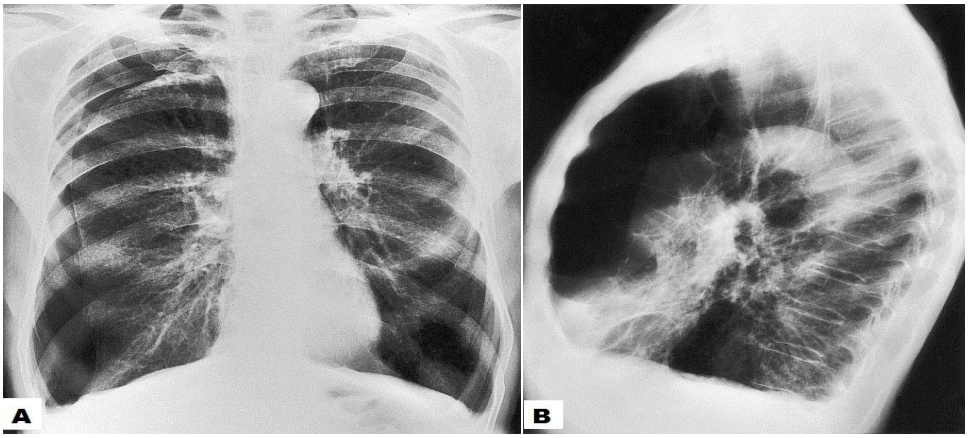


Figure. 1. Standard radiography (PA and profile) COPD phenotype emphysematous.

A: Chest x-ray, incidence of PA, with evidence of flattening of the right hemidiaphragm, its midpoint reaching the upper edge of the anterior arch of the rib 7. Narrow, verticalized cardiac silhouette.

B: Chest x-ray, profile incidence, with increased retrosternal hyperintransparency and enlargement of the retrosternal space, measuring 4.6 cm between the aorta and sternum, 3 cm below Louis's angle, extending up to 3 cm anterior to the diaphragm. Both costophrenic angles are obtuse and the hemidiaphragms are flattened.

High resolution computerized tomography (HRCT) is not routine investigation. The main modification highlighted is the *EMFIZEMA*, which can be of the centeracinar type (upper areas) and panacinar (lower areas) - Figure 2. This is evidenced by the presence of bubbles, areas of low density and diminished vascular pattern.

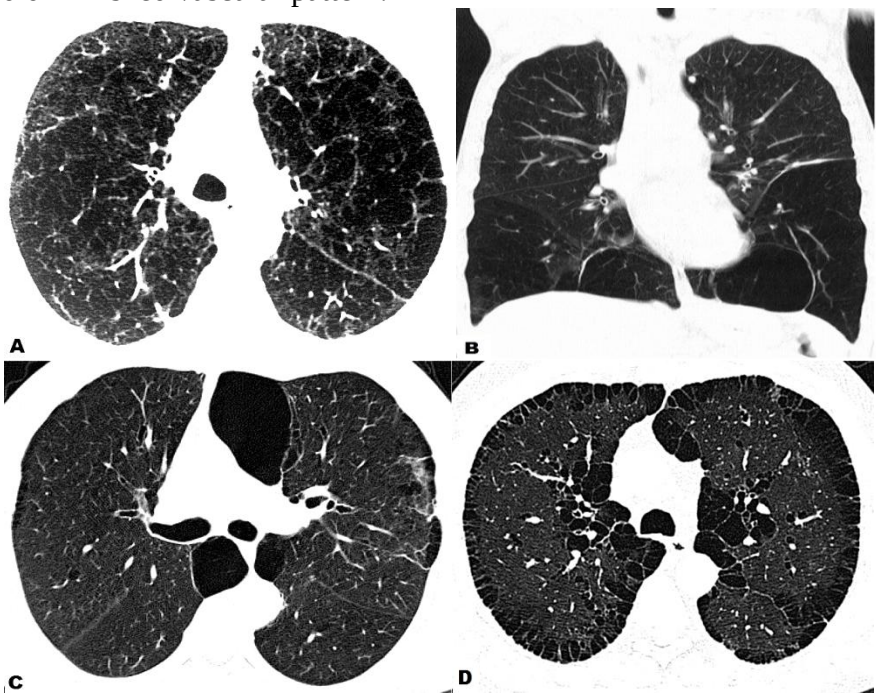


Figure 2. COPD HRCT aspect (MDCT): axial and coronary sections, with anatomical distribution of emphysema: A: centrolobular emphysema, B: panlobular emphysema, C: bulos emphysema, D: paraseptal emphysema

Positive diagnosis

It involves combining the presence of risk factors, age > 35-40 years, with clinical elements (cough, dyspnoea, decreased effort capacity) and spirometric certification of an irreversible or partially reversible obstruction after administration of inhaled β2-agonists (FEV1 <80% of the predicted value and FEV1 / CVF <70% of the predicted value).

Differential diagnosis

- *Hemoptysis* is an event that should bring into question pathologies such as bronchiectasis, neoplasm (in 12-22% of cases) or pulmonary thromboembolism (TEP). It is sometimes encountered in COPD exacerbations. The bronchiectatic disease is manifested by abundant purulent sputum and localized bronchial rales. The CT investigation is edifying. COPD in stage IV (risk class D) is complicated in 30-50% of cases with bronchiectasis.
- *Diffuse pulmonary fibrosis* should be taken into consideration when dealing with dyspnea without coughing, expectoration or wheezing. In this case, typical bilateral basal rallies "in velcro" are highlighted, often accompanied by digital hippocracy. The characteristic CT appearance is that of "honeycomb", "matte glass", fiber cross-linking with traction bronchectases, etc.
- *Obliterate bronchiolitis* comes into question in patients with rheumatoid arthritis or transplanted. The CT investigation is the one that will finally clarify the situation

- *NYHA IV heart failure* is confirmed by the lack of obstruction at the pulmonary level, the characteristic radiographic aspect and the presence of cracking rales at basal, bilateral level.
Great attention should be paid to the situation where COPD has reached the stage of decompensated Cor pulmonale.

Differential diagnosis *by primam* must be made with bronchial asthma (Tables 1 and 2).

Table 1. Differential diagnosis of COPD - asthma: anamnestic and clinical

	ASTHMA	**COPD**
Initial start	Predominantly in childhood	At maturity
Dyspnoea	Paroxysmal; reversible under treatment	Progressive, slightly reversible
Cough	Usually in crisis	Frequent, prolonged, chronic
Expectoration	±	Usually chronic
Cyanosis	rare	Frequent, in evolution
Symptoms at night	Relativ comune	Rare, unusual
Cor pulmonale	±	++
Effect of ICS treatment	Efficient	±
Evolution	In episodes	Progresive
Prognosis	Good; control > 80% of cases	Stagnation or slowing down of degradation

Table 2. Tests for differential diagnosis of asthma vs. COPD

Diagnostic tests	**ASTHMA**	**COPD**
Reversibility to bronchodilators with glucocorticoids	Usually present	Usually absent
Lung volume VR, CPT	Normal/low if reversible	High, usually irreversible
The diffusion capacity	Normal	Low
Hyperreactivity of the airways	High	It can be increased but is usually not measured due to airflow limitation
Allergic tests	Deseori pozitive	Often negative
Radiological	Normal	Modified in advanced stages
Sputum	Eosinophils	Neutrophils
Expired nitric oxide	High	Usually normal

Particular situations

Overlap syndrome Asthma-COPD (Asthma COPD Syndrome = ACOS, Asthma - COPD Overlap = ACO) is not classified as a distinct syndrome, but is defined as a limitation of airflow resulting from COPD and ASTHMA overlap. In approximately 30% of COPD patients, there is a significant reversibility of the post-bronchodilation airflow and other features of bronchial asthma can be noted, such as increased level of eosinophils in sputum or increased nitric oxide in the exhaled air. The diagnosis can be established this way: a COPD patient who meets 2 major criteria or 1 major criterion + 2 minor ones.

Major criteria: Intensive positive bronchodilator test (FEV1 increase ≥ 15% and ≥ 400 ml); sputum eosinophilia; history of asthma (before 40 years). **Minor criteria:** Positive bronchodilator test (FEV1 increase ≥ 12% and ≥ 200 ml); history of atopy; Increased IgE.

Treatment

Pharmacological and non-pharmacological treatment must be individualized and guided by a variety of factors: severity of symptoms, risk of exacerbations, comorbidities, economic level, response to treatment or the ability to use different types of inhalers.

The treatment objectives in COPD target the impact of the disease on the life of the patient both short and long term.

The reduction of the symptoms is targeted in the short term with: improvement of the symptoms; increased effort capacity; improving health.

The long-term objective is to reduce the risk: improving respiratory function and reducing the speed of decline; the prevention and treatment of exacerbations; reducing mortality.

The components of COPD treatment are

(I) Reduction of risk factors

(II) Management of stable COPD

a) Patient education

b) Pharmacological treatment, including long-term oxygen therapy

c) Non-pharmacological treatment: pulmonary rehabilitation, resection surgery a lung volumes, lung transplant.

(III) Management of exacerbations

(IV) Complex management of severe stages

(I) Reduction of risk factors

Identifying and reducing exposure to risk factors are important steps in prevention and treatment. Smoking cessation has a marked impact on the decline of lung function, being able to change the "natural history" of COPD, the earlier it occurs, the more effective it is. Thus, counseling, whether or not associated with specific pharmacological therapy (nicotinic substitution, varenicline, bupropion) represents the "minimal advice" (the 5-step program). Other factors are aimed at reducing or avoiding indoor air pollution, resulting from the burning of biomass for heating, as well as eliminating or reducing workplace exposure. *Influenza and pneumococcal vaccination* are specific and effective preventive interventions regardless of the stage of the disease for COPD exacerbations (EBA).

(II) Management of stable COPD

a) Patient education

Patient training is an essential component of an effective treatment. It has to include elements related to the recognition of exacerbations, chronic physical and psychological changes generated by the disease, risk factors, self-management and understanding of the importance of the adherence to the prescribed treatment.

In clinical practice, the adherence rate is relatively low, about 10-40%. A surprisingly large number (31%) of patients with bronchial asthma reported that they had intended to stop medication the moment they felt better. "Low adherence to inhalation therapy is the main cause of unsatisfactory results in COPD treatment".

b) Pharmacological treatment

The severity of COPD in the current classification (GOLD) takes into account both the degree of obstruction (FEV1) and the symptoms and frequency of exacerbations (Figure 3). The classification according to FEV1 assesses the degree of bronchial obstruction and has diagnostic,

prognostic and evolutionary monitoring value. Although by definition, FEV1 decreases irreversibly, the current GOLD strategy recommends choosing the pharmacological treatment only according to the degree of symptoms and the risk of exacerbation; pharmacological treatment is aimed at improving the symptoms, reducing the frequency and severity of exacerbations, increasing tolerance to exertion, etc.

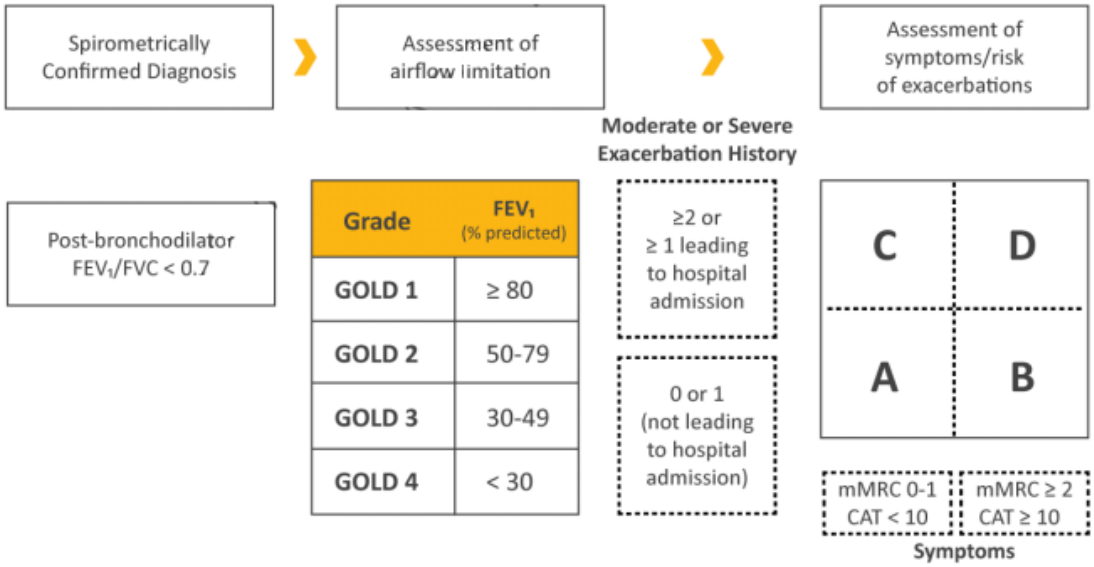


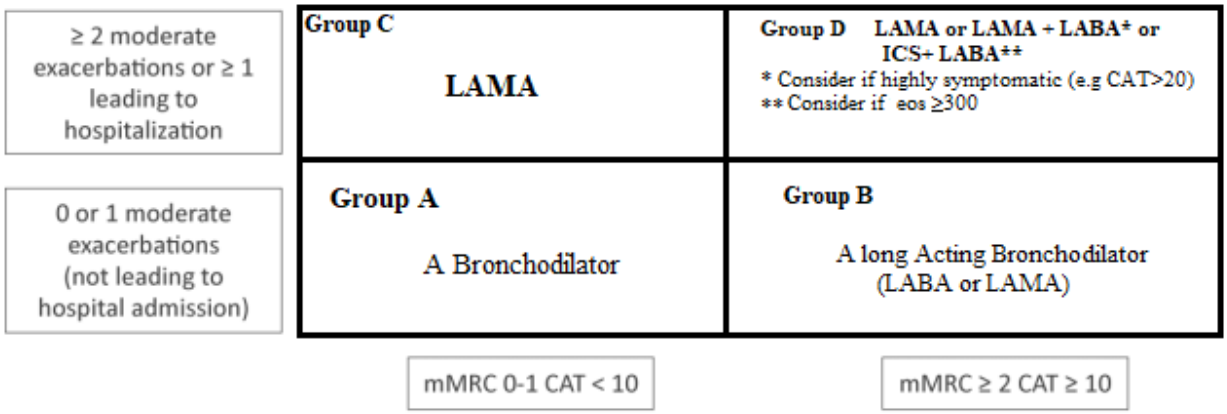
Figure 3. Assessment tool according to symptomatology and exacerbation risk (GOLD 2019)

Bronchodilators are the main treatment for this condition. They reduce dyspnoea / hyperinflation and increase the capacity of effort. The most used bronchodilators are divided into 3 classes: β2-adrenergic agonists (long / short term), anticholinergics (long / short term) and methylxanthines(Theophylline).

- *β2 short-acting agonists (SABA)* with rapid-acting effect and with action for 2-3 hours (eg Salbutamol). Used as inhaler as needed or prophylacticly (before exerting effort).
- *β2 long-term agonists (LABA)* "the true underlying medication in COPD" acts for a long period of time (12 hours) and the effect is rapidly installed (eg Formoterol); there are also β2 agonists with a long duration of 24 hours (eg Indacaterol).
- *Antimuscarinics (SAMA)* have a short duration of action for 2-3 hours (eg Ipratropium);
- *Long-acting antimuscarinics (LAMA)* act for a period of 12 hours.
-*Methylxanthines (Theophylline)* are weaker bronchodilators compared to those mentioned above; impose precautions for use, having a low threshold for the occurrence of side effects.

In stage I of the disease, **short- or long-term bronchodilators will be used, depending on the degree of dyspnea**. In the following stages, long-term bronchodilators, in single therapy or in various associations. The combination of a second bronchodilator with a different mechanism of action can improve the bronchodilator effect as well as the clinical one. Thus, patients on treatment with a bronchodilator and with persistent dyspnoea, will be added another bronchodilator (escalation of treatment). The combination of bronchodilators such as SABA / SAMA or LABA / LAMA bronchodilators increases the degree of bronchodilatation and reduces the risk of exacerbation. **Triple therapy** LABA + LAMA + ICS therapy addresses the risk category D for patients with elevated blood eosinophils > 300 cells / μL and with repeated exacerbations.

Inhaled corticosteroids (ICS) do not affect the progressive limitation of bronchial airflow, but reduce the frequency of EBA occurrence, and, as such, will improve the quality of life. ICS is recommended to be associated when the functional decline is advanced (FEV1 <50%) and in patients with ACO, eosinophilia or EBA. They will only be given in combination with long-term bronchodilators, and in doses exceeding the equivalent of 1000 micrograms beclomethasone, 2 times / day, in the form of combinations in use: salmeterol / fluticazone or formoterol / bedesonide.
The side effects of ICS are represented by oral candidiasis, dysphonia and the appearance of ecchymoses; At the same time, the risk of developing pneumonia increases significantly. Oral corticosteroids can only be used in the treatment of EBA, otherwise they do not benefit, on the contrary, they can have significant systemic adverse effects.



GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD. 2019. Available: http://goldcopd.org

Figure 4. Management of stable COPD; drug therapy; GOLD 2019

Long-term oxygen therapy (OLD)
Oxygen administration is the only proven pharmacological therapy that lowers the mortality rate. In hypoxemic patients, oxygen therapy improves mental capacity and tolerance of physical effort. OLD is indicated in COPD patients that present:
•PaO2 ≤ 55 mmHg or SaO2 ≤ 88%, with or without hypercapnia;
•PaO2 ≤ 60 mmHg or SaO2 ≤ 88% and signs of pulmonary hypertension, polycythemia (hematocrit > 55%) or heart failure.
The moment the blood gas concentration at rest is determined and the PaO2-SaO2 correspondence is evaluated, OLD can be started. The dosage of O2 needed in the state of rest will be increased by 1L / min, while sleeping and exercising. To be effective, the oxigen therapy needs to add up at least 16 hours a day.
Antibiotic: Macrolides.
Studies show that the administration of macrolides in the amount of 250-500 mg / day under 7/3 regimen reduces exacerbations in COPD. Azithromycin and erythromycin are also used for anti-inflammatory and immunomodulatory properties. COPD patients are frequently colonized with potential pathogens and the choice of antibiotics should be based on the antibiogram and the clinical status of the patient.
Other medications. Patients with viscous sputum and those who present repeated EBAs may benefit from mucolytics (erdostein, carbocysteine) and phosphodiesterase-4 inhibitors (roflumilast).

c) Non-pharmacological treatment

Pulmonary rehabilitation should start as early as stage 2 (GOLD B) and is included in standard treatment. The foundation of the rehabilitation consists in learning the techniques of diaphragmatic and pursed-lipped breathing. It includes physical training (endurance and strength exercises), education programs, nutritional intervention, psychological therapy and the development of energy conservation strategies.

The rehabilitation programs should start in the hospital (in-patient program). Upon their arrival at home, the patients should practice the techniques learned in the hospital.

Lung volume resection surgery and bronchoscopic techniques can ensure a better quality of life. Video-assisted interventions for reducing lung volumes are practiced in patients with massive emphysema located in the upper lobes. Endoscopic one-way valves can be implanted to reduce hyperinflation, etc.

Lung transplantation in cases of severe COPD can improve quality of life and functional capacity. The recommendation for transplantation includes patients with progressive accelerated form, which is not suitable for surgery or endoscopic interventions for lung volume reduction (FEV1 <15% with three or more severe exacerbations in the last period).

(III) Management of exacerbations

Exacerbation (EBA) is defined as the acute intensification of the symptoms (the expectorated volume increases, the sputum becomes purulent, the color turns and / or becomes fetid, the dyspnea worsens) and the inflammation in the airways is increased.

Exacerbations are highly debilitating events for the patient (by worsening of hypoxemia, increased resistance to airflow and consequently the effort to breathe - the mechanical work of the respiratory musculature, the increase of hypercarbia, pulmonary hypertension). Bacterial respiratory tract infections, air pollution, pneumonia, pulmonary thrombembolism, pneumothorax, inadequate use of sedatives or beta-blockers, heart failure, or arrhythmias are important factors in establishing EBA.

Hospitalization criteria in the intensive care units: with absolute indication in the presence: tachypnea (> 30 / min) or bradypnea (< 14 / min) associated with hypoxemia (PaO2 < 55% mmHg) or hypercapnia (PaCO2> 45%) and respiratory acidosis (pH < 35); paradoxical abdominal breathing, use of accessory respiratory musculature, tachycardia (> 110 / min), hemodynamic instability, arrhythmias, NYHA III / IV heart failure or consciousness disorder.

High-throughput oxygen therapy (up to 60L / min) will be administered to maintain a SaO2> 90%. At the same time, SABA ± SAMA ± ICS bronchodilators, systemic glucocorticoids and antibiotic therapy according to ABG will be used.

Non-invasive ventilation is the method of choice in the treatment of patients with acute respiratory failure with hypercapnia within the EBA who do not respond to drug treatment.VNI improves gas exchange, decreases the need for intubation, facilitates loading of respiratory muscles, improves respiration and improves respiration. .

(IV) Complex management of severe stages

Practicing energy conservation strategies and self-management are indispensable.

Comorbidities and systemic manifestations can influence mortality and hospitalizations, and their existence must be investigated routinely; when detected, specific treatment will be instituted according to the usual standards, regardless of the presence of COPD.

Evolution and prognosis

The evolution of severity in COPD is determined by the degree of dyspnoea, the extent of the obstructive syndrome, the hypoxemia and the overinfection with resistant bacteria. The presence of morning symptoms is associated with a higher risk of exacerbations, and with a decrease in daily physical activity.

Factors that may favorably influence COPD prognosis: smoking and exposure to passive smoking cessation, medication (bronchodilators, anti-inflammatories, antioxidants), long-term oxygen therapy (OLD) and participation in pulmonary rehabilitation programs.

Factors that aggravate the COPD prognosis: very low FEV1 (<30%); the presence of respiratory failure, PH and right heart failure, frequent EBA.

Complications: EBA, pulmonary neoplasia, pneumothorax, pulmonary hypertension and right heart failure completed in Cor pulmonale, sleep disorders, polyglobulin, pulmonary thromboembolic accidents.

The prognostic evaluation can be done by composite scores (multiple variable analysis), of which the most used is the BODE index (B = body mass index, O = obstruction - FEV1, D = dyspnoea - estimated by the mMRC scale, E = exercise, estimated by the distance traveled in the walking test for 6 minutes). High values (8-10) indicate a higher risk of death (80% over the next 28 months), low values (0-3) indicate a favorable prognosis.

Monitoring

An effective monitoring of a COPD patient implies a thorough therapeutic education and an action plan to prevent and early indentify EBAs. The patient`s inhalation technique should be evaluated at each visit.

Introduction to the second part of the chapter. Cor Pulmonale.

Definition

Over 70% of the cases of cor pulmonale (CP) are caused by COPD, asthma and bronchiectasis.

The chronic cor pulmonale appears in diseases that affect the function and / or structure of the lungs. It is defined by hypertrophy and dilation of the right ventricle, due to pulmonary hypertension (PH). The situations when these pulmonary alterations represent the consequence of diseases of the left heart or congenital heart diseases are exceptions.

The defining and diagnostic element of CP is right ventricular hypertrophy (RVH). This is an adaptive phenomenon produced by the chronic increase in pulmonary artery pressure, which is slowly settling. An average pulmonary artery pressure (PAPm) greater than 25 mmHg at rest or above 30 mmHg at exertion defines PH.

Epidemiology

The prevalence of CP is closely linked to that of the main causes of the pathologies. Chronic obstructive diseases, especially COPD and severe or chronic asthma account for over 70% of CP causes. WHO estimates that 14% of COPD patients have secondary PH.

Etiology

The most common causes of CP are diseases of the pulmonary parenchyma and intrathoracic airways. The main mechanism is hypoxic vasoconstriction.

A heterogeneous group of diseases cause CP: *neuromuscular diseases, disorders of the chest (kyphoscoliosis) and disorders of the control center of respiration*. The common factor in these pathologies is pulmonary hypoventilation with normal lung, which leads to the slow progressive and irreversible installation of PH by hypoxic mechanism and CP.

More commonly and more accurately diagnosed today are fibrous interstitial diseases and granulomatous diseases, which account for 15% of the causes of CP. They affect the alveolar structure and the pulmonary interstitium, resulting in loss of pulmonary capillary and exchange surface.

The causes and mechanisms of PH are varied. The classification of pulmonary hypertension (Dana Point 2013) can be divided into five groups. Of interest in this chapter is **Group 3** where pulmonary hypertension is due to pulmonary disease and / or hypoxia (Table 3).

Table 3. Diseases associated with the chronic lung heart

3. Pulmonary hypertension due to pulmonary disorders and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive disorders
3.4 Disorders of breathing in relation to sleep
3.5 Alveolar hypoventilation dysfunctions
3.6 Chronic exposure to high altitude conditions
3.7 Development anomalies

Pathophysiology

The chronic cord pulmonale is constituted by a variety of mechanisms that alter the pulmonary hemodynamics and function of the right ventricle.

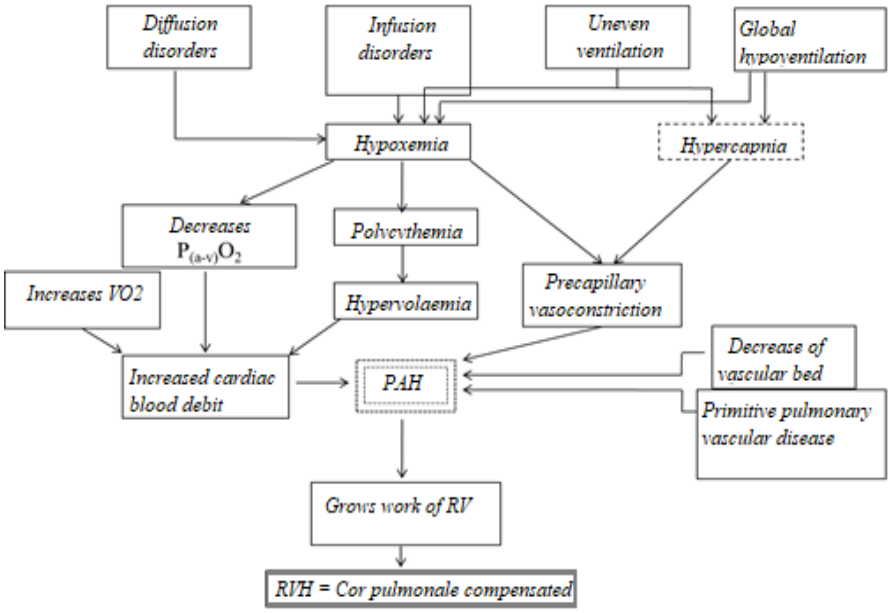


Figure 5. Mechanisms for constituting anomalies of gas exchanges (Tudor Sbenghe).

Hypoxic pulmonary vasoconstriction, chronic inflammation of the pulmonary artery wall, and anatomical reduction of the pulmonary vascular bed are the main mechanisms by which chronic pulmonary arterial pressure and pulmonary vascular resistance occur.

An important hypertensive pathogenetic mechanism in chronic obstructive pulmonary disease, thoracic deformities, neuromuscular diseases and interstitial lung diseases is alveolar hypoxia that induces vasoconstriction and hypertrophy of the media in the terminal pulmonary arteries. The level of PH correlates in particular with the degree of hypoxia and lung damage.

In hypoxic pulmonary regions, local pulmonary vasoconstriction appears as a homeostatic mechanism, which reduces blood flow to hypoventillated regions, causing shunt to regions with adequate ventilation. Acute alveolar hypoxia causes a direct pressor response on smooth arteriolar muscle cells (rapid and reversible effect on SaO2 normalization), while chronic hypoxia activates gene transcription factors and induces the release of mediators (prostaglandins, bradykinin, thromboxanes, cell growth factors) and proliferation of smooth muscle cells. Chronic inflammatory phenomena in the arterial wall and chronic hypoxia aggravates endothelial dysfunction with persistent vasoconstriction. In obstructive diseases, inflammation plays an important role in increasing pulmonary vascular resistance. During intercurrent infections, PAP worsens with the decompensation of the right heart.
In emphysema and pulmonary interstitial diseases the pulmonary vascular bed is reduced, but it is not sufficient to determine PH. However, the reduction of the pulmonary vascular bed in combination with hypoxia and inflammation may generate PH. Hypertrophy of the right ventricle is the consequence of chronic elevated pressure, and in more advanced stages, secondary to worsening PH, signs and symptoms of right ventricular failure appear.

Clinical manifestations

The clinical picture includes symptoms and signs of: Basic pulmonary disease that generates PH; PH syndrome and Cardiac changes with or without signs of right heart failure.
The clinical diagnosis of PH syndrome requires a high index of suspicion, being manifested only at very high pressure values. The association of exertional dyspnea, exertional syncope and precordial pain may suggest the presence of PH. Dyspnoea is the most common symptom. The syncope, usually at exertion, reflects the inability of RV to increase flow due to increased pulmonary vascular resistance. Chest pain (pulmonary artery angina) is a longer angina-like pain, which does not give up at rest or on nitroglycerin administration. This is due to the relative ischemia of the right ventricle (relative decrease of coronary perfusion, under normal vascular anatomy, of a dilated and hypertrophied RV). Hemoptysis can occur following a coughing effort due to rupture of the arteriole walls and dilated pulmonary capillaries, regardless of the etiology of chronic PH. Dry cough and dysphonia through compression of the laryngeal nerve by the dilated pulmonary artery may be present. However, the first manifestation of an PH may be sudden death.
The most characteristic elements of clinically CP implantation are cardiac changes as a result of PH. Right heart failure is the central element. Signs of systemic venous congestion are present: hepatomegaly with hepato-jugular reflux, turgid jugulars, peripheral edema, ascites. The extremities are hot, due to peripheral vasodilation, caused by hypercapnia.
The clinical examination reveals signs of hypertrophy and dilation of RV: left or subxifoid parasternal pulses, increased II noise in the pulmonary outbreak, possibly with inspiratory relief, diastolic pulmonary insufficiency (Graham-Steel) or systolic insufficiency.
The heart rate - sinus rhythm and tachycardic; extrasystoles and supraventricular tachyarrhythmias may occur in the presence of respiratory failure.
In the phase of cardiac decompensation the dyspnea is accentuated, the stasis is installed in the large circulation, the extremities become cyanotic and cold by reducing the peripheral blood flow or by hypoxemia and the xiphoid gallop appears. In severely decompensated forms, anasarca can appear.

Paraclinical explorations

Standard chest radiography objects suggestive changes for the etiological diagnosis: a) Modifications of central pulmonary arteries; b) Cord; c) Lung parenchyma.

a*) Changes of the pulmonary vessels:* The dilation of the pulmonary arteries is noted (main trunk and hilous arteries) in contrast to the attenuation of peripheral vascularization, with the appearance of peripheral oligohemia or the retention of distal vessels in severe PH. In the upper portion, the left middle cardiac arch can be curved due to the dilation of the trunk of the pulmonary artery. The presence of CP in COPD patients is associated with a diameter > 18 mm of the right descending pulmonary artery.
b) Changes of the heart: In the postero-anterior incidence the heart may appear enlarged overall by hypertrophy and dilation of the right heart that exceeds the left edge of the cardiac figure, with the lower right arch being pumped. In lateral incidence the cardiac silhouette is displaced anteriorly with the occupancy of the clear retrosternal space.
c) Changes in pulmonary parenchyma: In COPD (the most common etiology of CP) pulmonary hyperinflation, emphysema bubbles, reticular opacities and / or accentuated pulmonary pattern are detected; For diffuse or granulomatous interstitial diseases diffuse reticulonodular or reticulon images, predominantly perihilar or in the lower fields, are characteristic; linear opacities arranged bilaterally basal; lung "honeycomb".
Electrocardiogram. The diagnosis of CP can be considered accurate (almost 100% specificity) in the presence of ECG signs of right heart pressure overload (RVH and HAD).
RVH is manifested in ECG only in the advanced stages, when the electric vectors of the RV outnumber those of the LV. The absence of specific changes affecting the right heart does not exclude the presence of CP, the appearance of ECG can remain normal until the advanced stages of the disease.
Complex ventricular arrhythmias or supraventricular tachyarrhythmias are the consequence of changes in blood gases, hypopotassemia or drug overdoses (digitalis, theophylline, sympathomimetics).
Electrocardiographic changes in the chronic lung heart:
ECG criteria for CP with COPD: P-isoelectric waves in the DI or the right deviation of the axis; Aspect of pulmonary P (increase of amplitude of P wave in DII,DIII,AVF); Tendency to deviate from AQRS; R / S ratio in V6 ≤ 1; QRS microvoltage (QRS amplitude in standard and unipolar derivatives of members less than 15 mm); incomplete BRD (rarely complete).
The first 7 criteria are suggestive, but not specific; the last 3 are more characteristic for CP in COPD.
Echocardiography assesses the structure, the systolic and diastolic function of RV and the chamber size. It can also confirm the severity of PH and it highlights the left cardiac pathology generating PH (thus disabling the diagnosis of CP). The increment of the transverse diameter > 22-23 mm suggests RV dilation, and a value> 6 mm certifies RV hypertrophy. The paradoxical movement of the interventricular septum (SIV) to the left ventricle (LV) cavity is visualized in severe forms of RVH. Some abnormalities of pulmonary valve motility can be seen in COPD cases by COPD. Measurement of tricuspid valve travel as an index of contractility of RV is well correlated with FE of RV. In doppler mode, the systolic PAP can be determined by tricuspid regurgitation jet analysis.
Computed tomography (CT) investigates interstitial lung disease and suspected PET. CT with contrast substance administration may reveal dilated right heart cavities or enlargement of the pulmonary artery and visualization of the thrombus up to the sub-segmental arteries.
Nuclear magnetic resonance imaging (MRI) provides anatomical and functional RV data (mass, fatness, volume, FE%), as well as pulmonary vascularization data. It has a specificity of 98% in the detection of TEP.

Pulmonary artery catheterization directly measures pressure in the pulmonary artery and pulmonary hemodynamic parameters (pulmonary vascular resistance, pulmonary capilary pressure, cardiac output, etc.) and is the gold standard. Right catheterization can confirm the presence of PH and its quantification (PAPm> 25 mmHg at rest or> 30 mmHg at exertion).

Diagnostic

Formulating the positive diagnosis is relatively easy to establish in the presence of a history of pulmonary disease and the existence of symptoms and clinical signs of lung / heart disease. Based on ECG examinations and radiological examinations or pulmonary artery catererism, the signs of hypertrophy / dilation of the right heart and possibly of the enlarged pulmonary arteries in the hilum, confirm the suspicion.

Evolution. Prognosis

In chronic lung disease, CP development has a severe prognostic and mortality is high. Although these patients have slightly to moderately elevated PAP values, it is not clear whether PH is an underlying marker of disease severity or cause of mortality.

The evolution of CP within COPD is influenced by a number of factors such as: the rate of degradation of FEV1, the type of COPD, the frequency and severity of exacerbations. The prognosis worsens when the onset of right ventricular insufficiency (IRV) occurs. Mortality at 5 years after the first right heart decompensation in COPD is at 40%. The function of the right heart can be significantly improved by oxygen therapy.

The mortality of patients with increased PAP is higher compared to patients with normal PAP values. An increased risk for frequent and severe exacerbations presents COPD patients with a modest increase in PAPm (> 18 mmHg).

Rhythm disorders such as fibrillation or atrial flutter with rapid AV are common and are resistant to antiarrhythmic treatment. These can induce or aggravate insufficiency of the right ventricle (IRV).

For patients with interstitial lung disease in idiopathic pulmonary fibrosis, sarcoidosis and systemic sclerosis, CP is a predictor of mortality. Since there are no factors for reversibility of PH, once installed, right heart failure is refractory to treatment.

Treatment

The therapy of patients with CP primarily targets the pathology caused by PH (pulmonary or extrapulmonary), in addition to the treatment of reducing PH to prevent the installation of right heart failure. The general measures include: the abandonment of the funnel, the reduction of the excess weight, the diet hyposodate, the prophylaxis of the infections.

The treatment of the underlying disease causing PH mainly targets the etiological entities that have a degree of reversibility. In the case of COPD, the correct treatment represents the prophylaxis of CP and prevents its aggravation, by combating the episodes of exacerbation and the obstructive ventilatory dysfunction. In COPD patients, respiratory disturbances during sleep are common and may contribute to hypoxemia and nocturnal hypercapnia, worsening pulmonary vasoconstriction. The use of mechanical ventilation on the mask (CPAP) causes beneficial effects by improving the gas exchanges.

Oxygen should be administered for the purpose of preventing and treating CP in patients with chronic respiratory failure due to pulmonary disease with PH consecutively installed. Correction of chronic alveolar hypoxemia decreases pulmonary vasoconstriction by reducing pulmonary vascular resistance and improving right heart rate.

In very severe stages of COPD with PaO2 < 55 mmHg or SaO2 < 88%, regardless of the presence or absence of hypercapnia, long-term oxygen therapy (OLD) over 16 hours per day is indicated. Maintaining PaO2 > 60 mmHg and / or SaO2 > 90% is the therapeutic target. The OLD indication becomes valid in the presence of PH or of right heart failure at PaO2 values of 55-60 mmHg or SaO2 < 88%. Also, improvement of neuropsychological status and life quality is favorably influenced by OLD. The hemodynamic evolution is more stable with a decrease in cases of sudden death, especially at night.

Vasodilators are not routinely recommended in CP. Vasodilatory treatment is indicated in severe pulmonary hypertension from idiopathic PH or associated with collagenosis or interstitial lung disease. Favorable clinical results have shown Prostacyclines given i.v (epoprostenol) or inhaler (iloprost), with significant decrease in pulmonary artery pressure and pulmonary vascular resistance. It is effective in medium forms of PH, chronic treatment with Bosentan (endothelin receptor blocker) or in combination with prostacyclin derivatives in severe forms of PH.

Positive inotropic treatment is recommended only in CP associated with: supraventricular tachyarrhythmias, systolic LV dysfunction, right heart failure with low DC (significant signs of RVH, hypotension, retention due to prerenal mechanism). The doses of digitalis indicated are low (0.25 mg 5-6 times a week), the toxicity of digitalis being common in CP due to K depletion and myocardial hypoxia.

In acute right heart failure, treatment with non-digital positive inotropic substances (dopamine, dobutamine, phosphodiesterase inhibitors) is indicated.

Diuretic treatment is indicated in patients with manifested right heart failure and hydrosaline retention. The therapeutic benefits are represented by the improvement of the quality of life and the symptomatic effects, without the existence of studies that attest the improvement of the survival.

The administration of diuretics will increase the cardiac performance by decreasing the volume expansion and the RV preload, the pulmonary extravascular water is reduced and the pulmonary gas exchange is improved. Handle diuretics (Furosemide in doses from 40-80 mg / day to 500-100 mg / day in refractory forms) are used. The combination of anti-steroid diuretics (spironolactone in doses above 100 mg / day) potentiates diuresis and prevents potassium depletion.

Phlebotomy is performed in patients with marked secondary polycythemia (hematocrit> 55%), a result of chronic hypoxemia, to reduce pressure in the pulmonary artery and decrease pulmonary vascular resistance, improving exercise tolerance.

Surgery. Lung transplant is reserved for the terminal cases of irreversible disease or CP of primitive PH, idiopathic pulmonary fibrosis, histiocytosis X, cystic fibrosis, resistant to conservative treatment.

Atrial septostomy creates or enlarges the opening between the atria to allow the passage of a larger amount of blood from the left atrium to the right atrium.

Preventive measures

Prophylactic measures for the onset of CP are as follows: smoking cessation; avoiding exposure to gases and irritating substances by changing the workplace (when the situation requires it); weight loss; prophylaxis of infections (pneumococcal, influenza) by avoiding crowded areas in cold seasons with pneumococcal and influenza vaccination and proper treatment of all respiratory diseases.

Bibliography

1. Curs de Pneumologie pentru medicii rezidenți, sub redacția Voicu Tudorache, Editura Mirton 2013.
2. The Washington manual of medical therapeutics, 33rd edition, 2010, Chronic obstructive pulmonary disease, pg. 272-282,
3. Murray & Nadel's Textbook of Respiratory Medicine, 5th ed., 2010 Saunders, Elsevier
4. MacNee W, ZuWallack R.L., Keenan J., Clinical management of chronic obstructive pulmonary disease., Professional Communication. Inc., 2005
5. http://www.srp.ro/GOLD-Global-Initiative-for-Chronic-Obstructive-Lung-Disease-120.htm
6. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf
7. Ali, J., W.R. Summer and M.G. Levitzky (eds.), Pulmonary Pathophysiology, 3rd Ed, *McGraw-Hill, New York* 296 pp., 2010.
8. Tudor Sbenghe, Recuperarea Medicala a Bolnavilor Respiratori, Ed. Medicala 1983
9. Oxford handbook of Clinical Medicine, eighth edition, 2010., Chronic obstructive disease., pg. 176-178
10. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease, Bartolome R. Celli et al. N Engl J Med 2004; 350:1005-101
11. The TORCH (TOwards a Revolution in COPD Health) survival study protocol. The TORCH Study Group (J. Vestbo) Eur Respir J 2004; 24: 206–210.
12. Systemic effects of chronic obstructive pulmonary disease. A.G.N. Agusti, A. Noguera, J. Sauleda, E. Sala, J. Pons, X. Busquets. Eur Respir J 2003; 21: 347–360
13. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. GBD 2015 Chronic Respiratory Disease Collaborators. Lancet Respir Med. 2017 Sep; 5(9):691-706.
14. Tudorache V, Oancea C, Mlădinescu OF., Clinical relevance of maximal inspiratory pressure: determination in COPD exacerbation., Int J Chron Obstruct Pulmon Dis. 2010 May 6;5:119-23.
15. (5)Lowie E G W Vanfleteren, Martijn A Spruit, Emiel F M Wouters, Frits M E Franssen., Management of chronic obstructive pulmonary disease beyond the lungs., *Lancet Respir Med* 2016., Published online June 2, 2016
16. Textbook of Pulmonary Vascular Disease, Springer 2011 edition.
17. Murray and Nadel's Textbook of Respiratory Medicine, 5th edition.
18. Guidelines for the diagnosis and treatment of pulmonary hypertension, European Heart Journal (2009) 30, 2493–2537.
19. Hipertensiunea arterială pulmonară în practica de cardiologie, Carmen Ginghină, Editura Academiei Române, București 2010.
20. Pulmonary hypertension in interstitial lung disease, Behr J, Ryu JH., Eur Respir J. 2008 Jun; 31(6):1357-67.
21. Chronic cor pulmonale, Emmanuel Weitzenblum, Heart 2003;89:225–230
22. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease, Arcasoy SM, Christie JD, Ferrari VA et al, Am J Respir Crit Care Med 2003; 167:735–740
23. Pulmonary hypertension in COPD, Chaouat A, Naeije R, Weitzenblum E (2008), Eur Respir J. 2008; 32:1371–1385
24. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Chaouat A, Bugnet AS, Kadaoui N et al; Am J 2005; Respir Crit Care Med 172:189–194
25. Cor pulmonale: an overview, Budev MM, Arroliga AC, Wiedemann HP, Matthay RA; Semin Respir Crit Care Med 2003; 24:233.
26. Harrison Medicină Cardiovasculară, Joseph Loscalzo, editura ALL 2013
27. Manualul Merk de Diagnostic și Tratament, ediția XVIII, Mark H.Beers, Robert S. Porter et all
28. Pulmonary diseases and the heart, Han MK, McLaughlin VV, Criner GM et all 2009 -116(25):2992-3005
29. Incidence proportion of acute cor pulmonale in patients with acute respiratory disease - A systematic review and meta-analysis. Indian J Crit Care Med. 2017 Jun 16(6) 364-75

7. SUPERIOR AND LOWER RESPIRATORY TRACT INFECTIONS

I. Upper respiratory tract infections – BRONCHITIS

Bronchitis is characterized by inflammation of the mucosa lining the airways between the trachea and alveoli (bronchi). There are two forms of bronchitis: acute and chronic.

ACUTE BRONCHITIS

Acute bronchitis is a self-limiting infection of the large airways, which most often manifests through coughing with or without sputum production, which recovers after 2-3 weeks. Other signs and symptoms that can be encountered during acute bronchitis are: nasal congestion, dyspnea, oropharyngeal pain, headache, fever, myalgia, fatigue, wheezing.

Acute bronchitis is caused by viral infections in up to 90% of cases, bacterial infections being detected in 1% to 10% of cases. The viruses incriminated in the determination of acute bronchitis are rhinoviruses, adenoviruses, enteroviruses, Influenza virus, Parainfluenza virus, syncytial respiratory virus; the bacteria involved in the etiology of the disease are *Mycoplasma pneumoniae, Bordetella pertussis, Chlamydia pneumoniae, Streptococcus pneumoniae.*

The diagnosis is based on the clinical symptoms and signs. Acute bronchitis cough should be differentiated from chronic cough caused by other pathologies, such as asthma, chronic obstructive pulmonary disease, gastro-oesophageal reflux disease, heart failure, treatment with angiotensin-converting enzyme inhibitors or pneumonia.

The treatment of acute bronchitis is symptomatic, being primarily focused on cough suppression. Patients with dry cough are given antitussive (dextromethorphan) and those with productive cough are given expectorants. In the presence of nasal obstruction nasal decongestants may be administered, and non-steroidal anti-inflammatory drugs may be administered to patients presenting with fever, oropharyngeal pain, myalgia, headache. It is also important that patients have good hand hygiene, hydrate and quit smoking.

Antibiotic administration is limited given the predominantly viral etiology of acute bronchitis. These are recommended only in cases where bacterial etiology is suspected or confirmed. It is indicated the use of antibiotics in the macrolide class, in cures of 5-7 days. Excessive use of antibiotic treatment results in the development of resistant bacterial strains.

Even without treatment, most cases have a good evolution towards the resolution of symptoms.

CHRONIC BRONCHITIS

Chronic bronchitis is defined by the non-specific chronic inflammation of the bronchial wall, the consequences of which are coughing with expectoration for a period of at least 3 months a year, two years in a row. Smoking is the main risk factor for chronic bronchitis. Air pollution and occupational exposure also play an important role in the pathogenesis of the disease.

At first the cough is present only in the morning, and then it is permanent. Sputum is usually mucoserous, and during periods of infectious exacerbation it becomes mucopurulent. The presence of symptomatology is associated with a significant burden on the affected persons, whether or not these patients have obstructive syndrome.

Patients with chronic bronchitis have an increased risk of developing chronic obstructive pulmonary disease. The treatment aims primarily bronchial irritation reduced by quitting smoking, avoiding exposure to air pollutants and correct treatment of ORL infections.

Antitussives are indicated at the onset of bronchitis, subsequently, with the appearance of the expectoration, administering expectorants and mucolytics (by bone or in aerosols). Antibiotics are given during bacterial exacerbations. Patients should have adequate fluid intake, as proper hydration promotes fluidization of bronchial secretions.

II. Infections of the lower respiratory tract – PNEUMONIA

Definition

Pneumonia is defined as an acute infection of the alveolar and / or interstitial pulmonary parenchyma, caused by a variety of microorganisms (bacteria, viruses, fungi).
Pneumonias are classified as follows:

- Acute community pneumonia (CAP) - infections acquired in the outpatient setting;
- Nosocomial pneumonia (NP) - the infection occurs at least 48 hours after hospitalization; this entity is subdivided into pneumonia associated with medical care and pneumonia associated with mechanical ventilation;
- Pneumonia in the immunocompromised;
- Suction pneumonias.

Epidemiology

Pneumonia has a significant morbidity rate, being the main cause of mortality due to a worldwide infection.
The actual incidence of CAP is uncertain, because the disease is not reportable and only part of the cases require hospitalization (between 20% and 50% of cases). The estimated incidence of CAP varies between 2-15% cases / 1000 persons / year, with a higher rate in the elderly.
Although many patients can be treated by outpatient, the mortality among patients with CAP requiring hospitalization varies between 5-15%. The percentage increases up to 20-50% in patients requiring intensive care in the ICU.
CAP frequency is higher in cold season, often associated with influenza and other respiratory viruses.

Etiology

Pneumonia is an infection that can be caused by a large number of pathogens (over 100 germs have been identified).
Streptococcus pneumoniae is the most common pathogen in the etiology of CAP. Globally, up to 30% of the CAP is due to pneumococcal infection, regardless of age, followed by infection with *Haemophylus influenzae* and atypical microorganisms (*Mycoplasma, Chlamydia and Legionella spp*., Respiratory viruses - influenza virus, syncytial respiratory virus).
The most common causes of CAP in patients who do not require hospitalization are: *Mycoplasma pneumoniae, Streptococcus pneumoniae, Chlamydophila pneumoniae, Haemophilus influenzae* and respiratory viruses.
Up to 20% of the CAP with severe evolution is due to polymicrobial infections, which implies a combination of microorganisms. The most commonly incriminated pathogens that cause severe CAP (requiring ICU care) include: *Streptococcus pneumoniae*, gram-negative bacilli, *Staphylococcus aureus*, species of *Legionella, Mycoplasma pneumoniae*, respiratory viruses and *Pseudomonas aeruginosa* (variable frequency or absence in frequency risk factors).

The causative spectrum of nosocomial pneumonia also includes gram-positive cocci (S. aureus, S. pneumoniae), but more commonly NP are caused by gram-negative bacilli such as *P. aeruginosa, Klebsiella pneumoniae, Enterococcus coli*, and *Enterobacter spp*.
Multidrug resistance (MDR) is the result of the interaction of patient-specific risk factors and hospital units, such as the recent use of antibiotics, the presence of structural lung diseases, and the existence of resistant bacterial strains in the hospital. The commonly encountered MDR pathogens are methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa* and extended-spectrum beta-lactase secreting bacteria.

Pathogenesis / Risk factors

The production of pneumonia depends on three factors: microbial virulence, the size of the microbial inoculum and the host's defense capacity.
The mechanisms of defense of the respiratory tract are represented by mechanical mechanisms and biological mechanisms (humoral and cellular immunity). The mechanical mechanisms are responsible for the removal of large particles that are retained and expelled through the nasal cavity with the help of the muco-ciliary cleft and cough intervention. Alveolar macrophages remove small particles (<5 microns).
The contamination mechanisms of the lower respiratory tract are: aspiration, inhalation, hematogenous dissemination and direct inoculation. Micro aspiration from the oropharynx or nasopharynx is the most commonly incriminated mechanism in the pathogenesis of peonies, followed by inhalation of infected aerosols. Aspiration occurs during sleep and in healthy people, but progression to pneumonia is rare. Oropharynx of healthy individuals is colonized with various aerobic germs: *Streptococcus pneumoniae, Streptococcus pyogenes, Mycoplasma pneumoniae, Haemophilus influenzae, Moxarella catharralis*; anaerobic germs are found in the gingival groove and bacterial plaque.
Hematogenous dissemination occurs from distant infectious outbreaks (septic phlebitis, endocarditis). Direct inoculation by stabbing or trauma is rarely encountered in practice.
Risk factors involved in the development of pneumonia are: chronic alcoholism, drug use, consciousness disorders, swallowing disorders, smoking, chronic lung disease (COPD, bronchiectasis), immunosuppression, extreme age, neoplasia (especially pulmonary), HIV infection, malnutrition, nursing home residence, recent hospitalizations, comorbidities (cardiovascular or renal disease), poor dental hygiene.

Pathology

The pneumonic process is the result of the host's inflammatory response against microorganisms, representing an inflammation of the pulmonary alveoli. Lobular pneumonia has four evolutionary stages, characterized by alveolar changes.
The *stage of congestion* that lasts less than 24 hours. Histological examination reveals dilated alveolar capillaries, and in the alveoli there is a sero-albuminous (protein) exudate containing several red blood cells, leukocytes and causative germs.
The *stage of red hepatization* is characterized by the presence of a sero-fibrinous exudate in the alveolar spaces in which erythrocytes and neutrophils are present; at this level a fibrin network is created in which numerous pneumococci can be detected, some of them being about to be phagocytosed by neutrophils.

The *gray hepatization* stage begins after 2-3 days. At this stage the intra-alveolar migration of leukocytes (initially neutrophils, then macrophages) takes place and the filling of the alveoli with a large amount of fibrin.
The *resolution* is characterized by the presence of an uneven and progressive process of liquefaction of fibrinous exudate from the airspace. Fibrinolytic leakage is due to fibrinolytic enzymes released by senescent neutrophils. Macrophages are the predominant cell type, having a role in phagocytosis of senescent cells.

Clinical manifestations

Acute community pneumonia can take two clinical forms: "*typical" pneumonia* and *"atypical" pneumonia*. This classification is used to guide the choice of empirical therapy according to the likely pathogens involved in the production of the disease.
The clinical picture of *"typical" pneumonia* is determined by bacteria such as *S. pneumoniae, H. influenzae* and *K. pneumoniae*. The onset of the disease is acute, brutal, manifested by high fever, inaugural shivering, productive cough with muco-purulent or hemoptotic sputum, dyspnea, pleuritic chest pain and clinical signs of pulmonary condensation. The pleuritic pain of "thoracic juncture" character changes its intensity according to position and is amplified by the deep breath and cough. The pulmonary condensation syndrome is characterized by the presence of the percussion maturity, the amplification of the vocal vibrations, the diminution of the vesicular murmur, the tubal breath and the presence of the cracking rales; these manifestations are present in only 1/3 of the patients admitted with radiologically confirmed CAP. The clinical picture described above, associated with a radiological image of lobular or segmental condensation defines lobular frank pneumonia. In the elderly, the symptoms may be greatly diminished and the febrile syndrome appears less frequently due to the diminished response of inflammatory cytokines (especially TNF-α); in this group of patients, on the other hand, it can be observed the alteration of the mental status (confusion, disorientation, hallucinations).
When the fever is high, persistent and accompanied by solemn shivers, the onset of a bacteremia outbreak should be suspected; In these situations, cardiovascular phenomena (tachyarrhythmias), arthralgia, impotence, myalgia, fatigue or malaise may also be present.
Symptoms of *"atypical" pneumonia* are secondary to infection with *M. pneumoniae, C. pneumoniae*, *Legionella* and viruses. This pneumonic form is characterized by a slow progressive onset in 2-3 days, being preceded by signs of upper respiratory tract infection (rhinitis, otitis, pharyngitis), fever without chills, cough without expectoration, diffuse crackles and extra-respiratory manifestations (headaches , myalgia, hepatitis, cold agglutinins).

Severity assessment

The proper assessment of the severity of CAP cases is very important. A proper assessment of the patient's condition identifies the serious cases that cease treatment in the hospital, thus reducing the mortality rate.
Severity scores, such as the CURB65 score and the ATS / IDSA scale, assist the clinician in evaluating patients.
The **CURB65 scale** comprises 5 criteria to be analyzed, being stratified from 0 (no criteria) to 5 (all criteria). This score is simple and easy to apply in clinical practice.

Table 1. CURB65 scale

	Clinical	Points
C	Confusion	1
U	Urea ≥ 42 mg / dL	1
R	Respiratory rate ≥ 30 / min	1
B	Systolic blood pressure <90 mmHg or Diastolic blood pressure ≤ 60 mmHg	1
65	Age ≥ 65 years	1

Table 2. Risk score CURB65

Score	Patient care location
0	Ambulatory
1	Ambulatory
2	Short hospitalization
3	Hospital
4/5	Hospital / ICU

The CURB65 score also allows stratification of the risk of death within 30 days. The higher the score, the risk of mortality increases; thus a score of 2 requires hospitalization of the patient. The **ATS / IDSA** (American Thoracic Society / Infectious Diseases Society of America) developed criteria for transferring ATI to patients with pneumonia who are not in shock or respiratory failure (Table 3). The presence of any major or three minor criteria is an absolute indication for the hospitalization of the patient in the ATI section.

Table 3. Criteria for transfer in the ICU section

Minor criteria	Major criteria
Respiratory frequency ≥ 30 / min	Need for mechanical ventilation
Tachycardia (> 125 / min)	
Multilobar or bilateral (Rx)	Septic shock requiring vasopressors
Hypotension requiring vascular filling	
PaO2 / Fio2 ≤ 250 or SaO2 ≤ 90% in room air *	
Acidosis (pH 7.30)	
Confusion and / or disorientation	
Urea> 20 mg%	
Leukopenia < 4000 / mmc or extreme leukocytosis:> 20,000 / mmc	
Thrombocytopenia < 100,000 / mm3	
Hypothermia < 36 C	
Hyponatremia (Na < 130 mEq / L)	
Hypoalbuminemia (serum albumin < 3.5 g%)	

*FiO2 (fractional concentration of oxygen in inspired gas)

Paraclinical examinations

In the case of patients suspected of pneumonia, paraclinical investigations should include the carrying out of hemolymphograms, biochemical tests for the evaluation of renal function, liver, arterial gasometry, acute phase reactants (C-reactive protein, procalcitonin), hemocultures, pleural fluid examination, bacteriological examination urinary antigen testing.

CBC usually shows leukocytosis with neutrophils; also the value of lymphocytes should not be omitted. Neutrophilia associated with lymphopenia are associated with severe infections and bacteremia.

A C-reactive protein (CRP) value below 20 mg/L when presented to a patient, associated with the presence of symptomatology over 24 hours, makes the diagnosis of pneumonia unlikely; In contrast, at a CRP level above 100 mg/L, the diagnosis of pneumonia is likely. Chest radiography can confirm the diagnosis in case of uncertainty.
Procalcitonin (PCT) is present in high concentrations in people with bacterial infections. This biological marker is increasingly used in the diagnosis of pneumonia; it is also useful in assessing the severity, prognosis and evolution of the disease, as well as in guiding antibiotic treatment. The administration of antibiotic treatment depending on the serum level of PCT decreased the average duration of treatment from 8 to 4 days. CRP and PCT are equal in predicting mortality risk, if they are also associated with the CURB65 scale. In elderly patients CRP is a better marker in predicting pneumonia than PCT.
Hemocultures are harvested in a febrile burst. Even if less than 20% of CAP cases are positive, a positive blood culture establishes the etiological diagnosis of pneumonia.
Urinary antigen testing for *S. pneumonia* and *Leginella pneumophila* may be useful in some patients, especially if sputum cannot be obtained or antibiotic treatment has begun; the antigen can be detected in the urine from the first day of the disease and for several weeks thereafter.
Performing bronchoscopy to obtain an endotracheal aspirate or bronchoalveolar lavage fluid for culture is reserved for patients with a severely affected general condition, admitted to the ATI section or immunosuppressed.
Table 4 summarizes the microbiological investigations recommended in patients with CAP.

Table 4. Microbiological investigations recommended in adult patients with CAP requiring hospitalization

Microbiological investigations *	Comments
Hemocultures	2 sets of hemocultures obtained prior to the initiation of antibiotics
Sputum	Valid sample, which will be stained Gram, and seeded
Sputum - if an anamnestic and radiological pulmonary tuberculosis is suspected	Colored smear Ziehl Nielsen, Gene expert analysis, seeding on Loewenstein -Jensen medium
Sputum - if an endemic mycosis is suggested anamnestically or radiologically	Medium smear and cultures Sabouraud
Sputa - anamnestic or radiological is suggested the presence of Pneumocystis jirovecii	Pneumocystis cysts on smear examined by silver staining or by immunofluorescence
Urine antigen test pneumococci	Sensitivity: 50-80%, Specificity > 90%
Legionella urinary antigen test	Sensitivity: 60-80%, Specificity> 95%
Sputum - for Legionella	Culture or PCR ** for Legionella Sputum
Sputum, bronchial secretion, bronchoalveolar lavage	PCR for Mycoplasma pn., Chlamydia pn, Legionella, viruses
Pleural fluid	Bacteriological, biochemical, cytological evaluation

* Infectious extrapulmonary outbreaks should also be investigated; ** PCR - polymerase chain reaction.

Radio-imagistic examination

Radioimagistic examination plays a central role in the management of the CAP. With the help of radiological images, the diagnosis of pneumonia is supported and the response to the treatment is evaluated. Another role of imaging examinations is to identify pre-existing pathological

conditions that promote and maintain lung infections. The imaging methods used to quantify and evaluate the evolution of pneumonia are *chest radiography, chest CT* and *chest ultrasound*.
Chest radiography is the first-intention investigation, being useful for confirming the presence and localization of the pneumonic process; it also quantifies the presence of pleural effusion or other pulmonary lesions.
Classically, three basic imaging models are described: *consolidation* (alveolar, non-segmental conduction, lobar pneumonia), *peribronchial nodules* (lobular, segmental consolidation, bronchopneumonia) and *"ground glass" opacities* (interstitial pneumonia).
Lobular pneumonia is defined as a process of pulmonary condensation, predominantly alveolar, with non-segmental distribution, usually single, homogeneous, of subcostal intensity, with diffuse or linear contour (given by the anatomical scissural limit), with aerial bronchogram, which may affect almost entirely one lob or more; the surrounding tissues, lung and thoracic volume are not altered by the pneumonic process.
Bronchopneumonia or *lobular pneumonia* is characterized by the presence of opacities of different dimensions, multiple, with segmental distribution, of subcostal intensity, with relatively inaccurate delimited contour, without visible air bronchogram and with tendency to confluence. The infectious process, due to the bronchogenic dissemination, has a central distribution along the peribronhovascular axis; from the topographic point of view it presents a non-homogeneous, diffuse distribution, with the interest of several pulmonary zones, thus determining the alternation of the pulmonary condensation zones with the free ones.
Interstitial pneumonia presupposes the presence of inflammatory infiltrates at the level of the distal interalveolar and peribronchial intestinal septa, associated with the partial filling of the alveolar space, which achieves a characteristic "ground glass" appearance. The radiological aspect may be of diffuse focal opacities, with reduced intensity of “veil” that correspond tomographically with the areas of partial alveolar condensation or aspect of reticular/reticulo-nodular opacities in the case of the predominance of interstitial lesions. Interstitial infiltrates can be located in a single lobe bilateral or bilaterally diffuse.

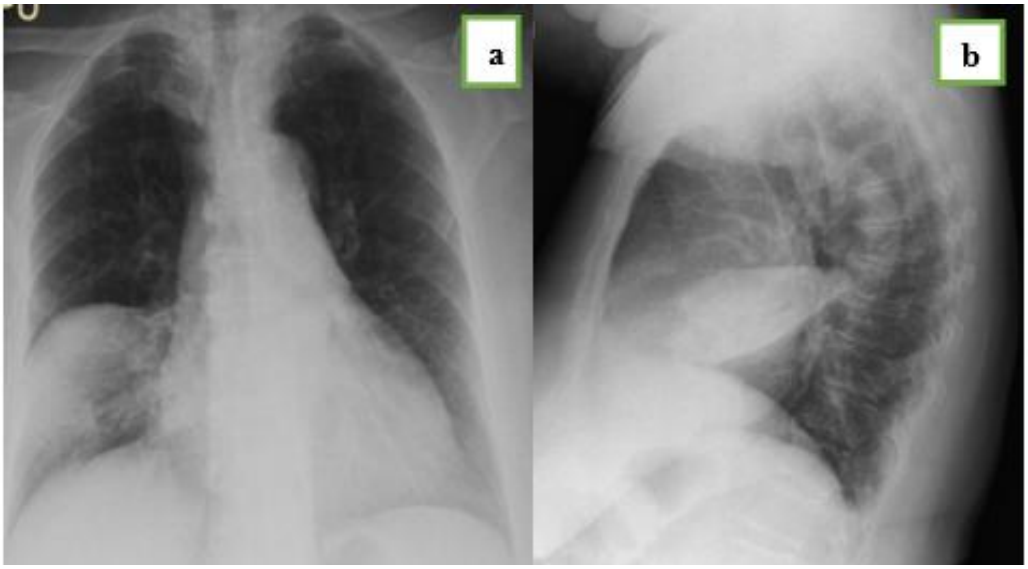


Figure 1. Chest x-ray postero-anterior incidence (a) and profile (b) Medium right lobular pneumonia highlighted as dense opacity, of subcostal intensity with net, linear contour, given by the anatomical scissural line.

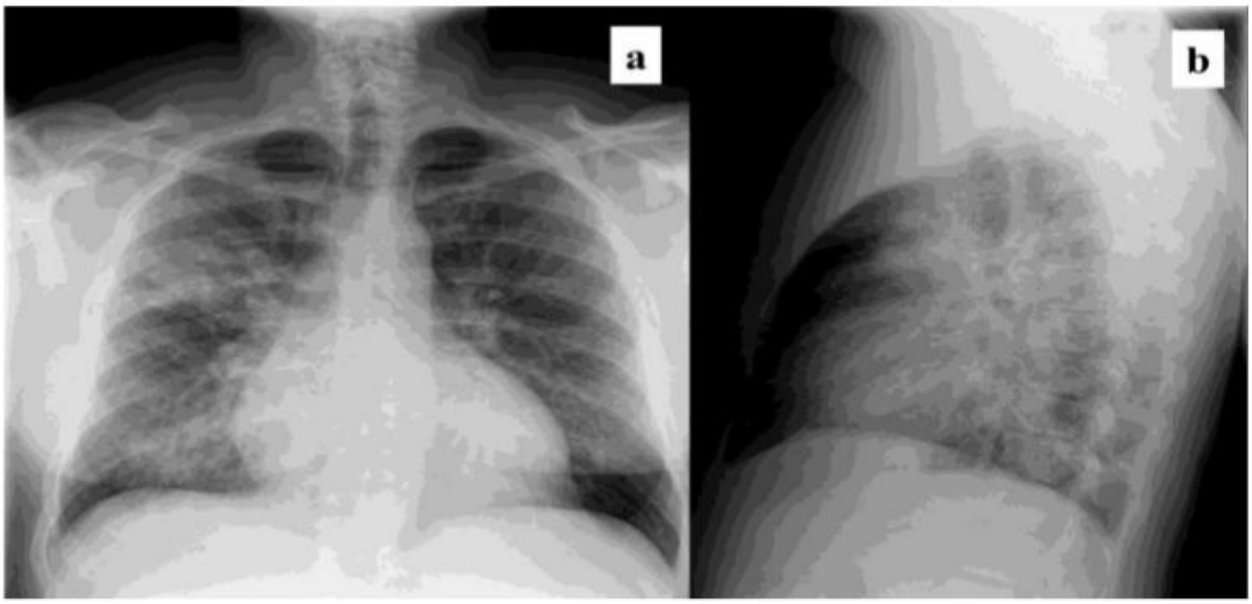


Figure 2. Postero-anterior (a) and profile (b) chest radiographs. Bronchopneumonia characterized by the presence of multiple opacities with segmental distribution, diffuse delimited, of subcostal intensity, projected in the upper central region and right infrahilar.

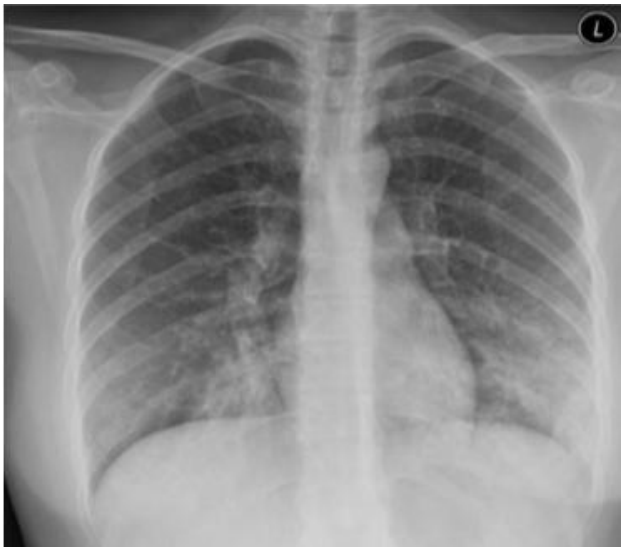


Figure 3.Postero-anterior chest x-ray – shows multiple reticular opacities and peribronchovascular alveolar infiltrates characteristic of interstitial pneumonia.

High-resolution computed tomography (*HRCT*) is a diagnostic method superior to pulmonary radiography. HRCT identifies the precise distribution of lesions in relation to the secondary pulmonary lobe. The infectious process appears either as a lobular condensation, with diffuse or linear contour, with present air bronchogram (lobular pneumonia), or multiple focal, lobular, diffuse contoured condensations appear, which may interest several segments or lobes, bilaterally, with a tendency to confluence, without airway bronchogram (bronchopneumonia).

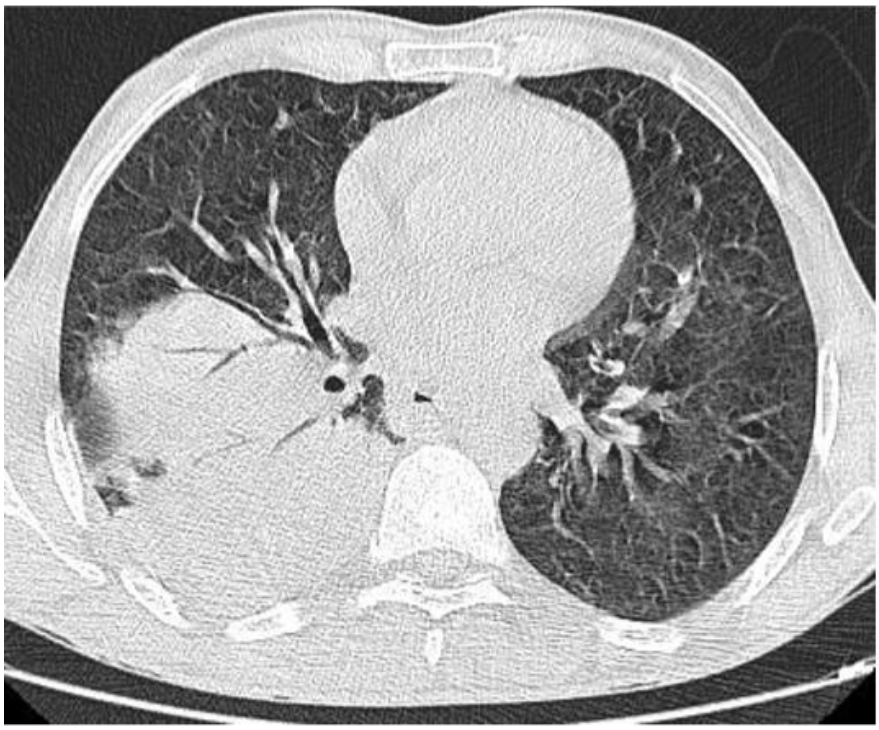


Figure 4. Chest CT, pulmonary window: RUL alveolar condensation, with aerial bronchogram present.

Chest ultrasound is a non-irradiating, repetitive imaging method that can be performed on the patient's bed. It is useful both in the diagnosis of pneumonia and in monitoring the progression of the disease. In the phase of setting up the pneumonic process, ultrasound alveolo-interstitial changes with appearance of multiple B lines (vertical reverberation artifacts starting from the pleural line), focal; this aspect is also encountered in the resorption phase of the condensation process.

The pneumonia constituted is presented ultrasound as an echogenic zone in the subpleural pulmonary space, with punctiform or trabecular hyperecogenities that correspond with the aerial bronchogram. Ultrasound changes before the appearance of radiographic lesions.

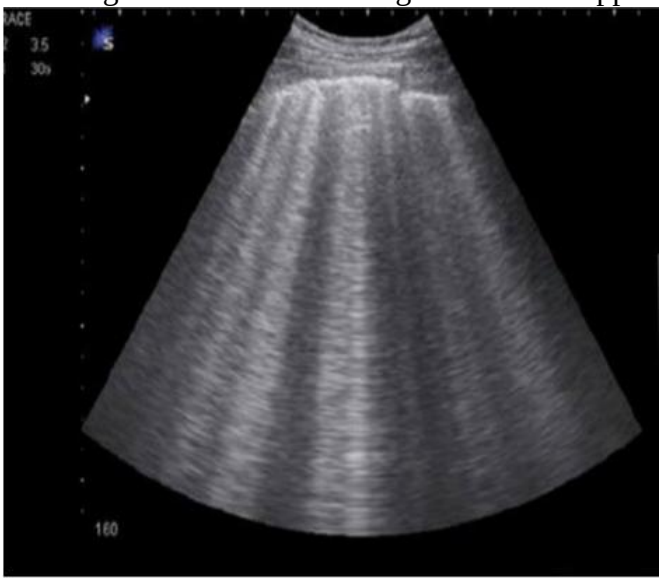


Figure 5. Pulmonary ultrasound. Multiple lines B in the resorption phase of a pneumonic process.

<u>Positive diagnosis</u>

The diagnosis is based on the patient's history, symptomatology, pulmonary radiological examination and paraclinical investigations. The bacteriological examination of sputum and hemoculture establish the etiological diagnosis of pneumonia. The CAP was divided into typical pneumonia and atypical pneumonia in order to guide the clinician in predicting the likely pathogens involved and selecting

an appropriate empirical therapy (Table 5). Thus, a rapid orientation according to the clinical-radiological picture of the CAP, may suggest the category of germs possibly involved and the establishment of the appropriate treatment as soon as possible:

- Systematic alveolar syndrome (condensation syndrome) → *Streptococcus pneumonia*;
- Non-systematic alveolar syndrome → *Legionella pneumophila*;
- Interstitial syndrome → *Atypical germs*.

Table 5. Elements of differentiation of alveolar CAP from interstitial CAP.

	Typical pneumonia (Alveolar)	**Atypical pneumonia (Interstitial)**
Patients	Usually - affected	Usually - normal (child, young)
Epidemic context	Absent	Often present (period of viral epidemic)
Pathogens more often incriminated	*Streptococcus pneumoniae, Haemophilus influenzae, Strept. pyogenes, Staph. aureus, Moraxella catarrhal, Ps. aeruginosa*	Atypical germs: *Mycoplasma pneumoniae, Chlamydia pneumoniae*, respiratory syncytial virus, influenza virus.
Debut	Suddenly (hours)	Progressive (days)
Shiver	Solemn	Rare
Fever	Over 39-40^{0}C	Below 39^{0}C
Chest joint	Frequent	Rare / absent
Cough	Productive	Dry
Sputum	Mucopurulent	Absent / sero-mucous
Herpes labial	Frequently	Rare
Objective examination	Condensation syndrome	Normal / bronchial rays
Rx. pulmonary	Systematized alveolar opacity, unilateral + pleural involvement	Bilateral interstitial infiltrate, unsystematized + alveolar involvement
Biological markers	Leukocytes> 15.000 / mmc, CRP> 60 mg / l, Procalcitonin> 0.5 µg / l	Leukocytosis <10.000 / mmc, CRP < 20 mg / l, Procalcitonin < 0.1 µg / l
Hemoculture	Usually positive	Negative
Sputum examination	Predominant PMN / pneumococcus	Saprophytic bacterial flora
Antibiotic response	Fast	Slow or absent

Differential diagnosis

Acute community pneumonia must be differentiated by multiple pathological entities such as:

- *Acute tracheobronitis* - manifests through coughing with or without expectoration, oropharyngeal pain, sometimes fever. The x-ray is normal, does not require antibiotic treatment and the prognosis is good.
- *COPD in exacerbation* - history of smoking, long-term dyspnea, cough with mucopurulent expectoration, hypoxemia, sometimes fever; radiologically, hyperinflation is detected; negative bronchodilator test ≤ 12%, VEMS / FVC <0.7 of the predicted value.
- *Bronchial asthma in crisis* - the presence of specific symptoms, positive bronchodilator test ≥ 12% and 200 ml, wheezing detected at auscultation, good response to corticosteroid administration.
- *Viral pneumonia* - occurs in epidemiological context; clinically the pharyngeal catarrh and herpes are detected; radiologically there is a discrete accentuation of the broncho-vascular drawing.
- *Fungal pneumonia* - occurs in immunocompromised people; symptomatology is low, uncharacteristic; thoracic CT can reveal an imaging kaleidoscope (nodules, pseudobronchopneumonia, the sign "halo", "matte glass", etc.); responds to antifungal medication.
- *Pulmonary abscess* - radiological image characteristic of cavity with hydro-aerial level; it starts as pneumonia, but evolves under treatment.
- *Pulmonary tuberculosis* - imaging aspect of nodular/excavated infiltrates located predominantly in the upper lobes; BK positive bacteriological examination; slow remission of lesions under antituberculosis chemotherapy.
- *Bronchopulmonary neoplasm* - thoracic CT and bronchoscopy are essential in establishing the diagnosis; may be accompanied by secondary retrostatic pneumonia.
- *Eosinophilic pneumonia* - relatively good general condition, blood eosinophilia; radiologically there is evidence of leaky infiltrates that have appeared in parasitic infestation, autoimmune diseases; good response to corticosteroids.
- *BOOP* (obliterating bronchiolitis with pneumonic organization) - appear in the context of connectivity or autoimmune diseases; radiologically detect alveolar condensations sensitive to corticosteroids.
- *Bronchiectasis* - characteristic chest CT appearance; history of bronchial suppurative syndrome.
- *Pulmonary thrombembolism* - symptomatic presents with pleuritic pain, dyspnea, fever, cough, thus being confused with pneumonia; appears in a favorable context (deep vein thrombosis); high scores on Wells or Geneva scales, high D-dimers; in the case of a pulmonary infarction, hemoptotic sputum, tachycardia, hypoxemia are detected; it should be borne in mind that the pulmonary infarction can become infected, causing veritable pneumonia.

Treatment

Ideally, the treatment of pneumonia should be done with an antibiotic that has the spectrum of action targeted on the pathogen involved in determining the disease. Because pathogens are rarely or late identified (20-30% of patients do not produce an interpretable sputum sample, and another 20-30% of pneumonia patients received antibiotic treatment prior to pneumonia evaluation), initial treatment for pneumonia patients is empirical. In the selection of empirical antimicrobial therapy, physicians should take into account the pathogens most commonly involved in the respective epidemiological context, the environment in which the pneumonic process appeared (in the community, hospital, nursing home), the severity of the disease, the age of the patient, the presence of comorbidities, the patient's immune status and previous (recent) antibiotic therapy. The recent use of an antibiotic increases the probability of developing pneumococcal strains resistant to the respective antibiotic or to a class of antibiotics. In these cases it is recommended to avoid antimicrobial treatments given up to 90 days before the diagnosis of pneumonia.

With the help of the risk scales, it will be decided the location where the patients will receive the specific treatment (ambulatory, hospital, ICU section). It should also be taken into account that the etiological spectrum is very wide, always changing, due to factors such as: aging of the population with the association of comorbidities, identification of previously ignored causal germs, increasing the incidence of patients with immunodepression, increasing the incidence of antibiotic resistant pathogens (penicillin-resistant pneumococcus, methicillin-resistant staphylococcus, gram negative).

Antibiotic treatment should be started as soon as possible after the diagnosis has been established. A short delay in starting therapy in favor of performing diagnostic procedures is reasonable in patients who are not hypotensive, but delaying treatment by one hour reduces the survival rate by 8%, and septic shock can be installed during the first hour after hypotension is installed. The diagnosis should be made within a period of 4-8 hours, the delay of the administration of the treatment over this time period will increase the hospitalization period and the mortality rate.

The choice of empirical treatment should be based on the recommendations of the guides updated according to the bacterial ecology of the respective country, as well as the location where the treatment is administered. Below we will outline a cumulative scheme with the recommendations for choosing the empirical therapy elaborated by the international societies of pneumology, infectious diseases and epidemiology (table 6).

Table 6. Empirical therapy recommended for adult pneumonia, depending on the place of treatment and clinical severity.

The location of the treatment and the severity of the disease	**Stable patients, not hospitalized** Low severity	**Patients requiring hospitalization** Medium/high severity	**Patients requiring hospitalization in the ICU section** Increased severity/ critical condition
Complexity of therapy	Antibiotic alone	Monotherapy or combination of antibiotics	Antibiotic association
ATS / IDSA Guides	Macrolides (azithromycin or clarithromycin) or (alternative) Doxycycline	β-Lactam (ampicillin, ceftriaxone, cefotaxim) + macrolides or (alternative) Respiratory fluoroquinolones (moxifloxacin, levofloxacin, gemifloxacin)	β-Lactam (ampicillin-sulbactam, ceftri-axone, cefotaxim) + macrolides or (alternative) β-Lactam + fluoroquinolones
ERS/ESCMID Guides	Amoxicillin or Tetracycline or (alternative) Macrolides	Aminopenicillins ± macrolides or (alternative) Respiratory fluoroquinolones	Third generation cephalosporins + macrolides or (alternatively) Third generation fluoroquinolones ± third generation cephalosporins (cefotaxim, ceftriaxone)

ATS: American ThoracicSociety; IDSA: Infectious Diseases Society of America; ERS: European Respiratory Society; ESCMID: European Society for Clinical Microbiology and Infectious Diseases

The duration of administration of antibiotic treatment should be as short as possible, where possible, to reduce the occurrence of resistance through the phenomenon of selection. In general, the duration of treatment is 5-7 days in stable cases, being prolonged in severe cases.
The clinical and biological evolution (leukocytes, PCT, CRP) should be constantly evaluated. If the progression is good after 3-5 days of treatment, it can be changed from intravenous administration of antibiotic therapy to oral administration (Table 7). De-escalation of the antibiotics used may also be considered. In patients with low severity, oral treatment is preferred.

Table 7. Criteria for switching from intravenous to oral administration of antibiotic treatment in acute community pneumonia.

Able to ingest medication;
Heart rate < 100 / min. and systolic blood pressure > 90 mmHg;
O_2 saturation > 90%, PaO_2> 60 mmHg in ambient air or low oxygen through nasal cannula, or return to initial oxygen level in patients who have undergone long-term oxygen treatment;
Respiratory frequency < 25 breaths / min;
Return to basic clinical status;
Temperature < 38.3^0 C.

Note: All criteria should be met within the last 24 hours prior to oral medication administration.

Other drugs used in the treatment of pneumonia are non-steroidal anti-inflammatory drugs (thoracic junction, hyperpyrexia), mucolytics, bronchodilators (provide airway permeability), antitussive (exhausting cough) and oxygen therapy (respiratory failure).

Evolution. Prognosis. Complications

The evolution of a pneumonia depends on several factors such as: the causative agent (inoculation, virulence), the timeliness of starting a targeted therapy, the patient's immune field, age and existing comorbidities. Under appropriate treatment (antibiotic therapy) the evolution is generally favorable, with the gradual remission of the symptoms and normalization of vital signs. Young patients without comorbidities recover completely within 2 weeks; elderly and patients with other comorbidities require a longer time to heal. If the evolution is slow, the clinical symptoms persist or worsen, it is necessary to review the case and to diversify the diagnostic methods to identify adjacent complications or comorbidities (pulmonary neoplasm, diabetes, immune deficiencies, pleurisy, etc.). Also, in these cases, antibiotic therapy must be re-evaluated. Certain conditions such as smoking, old age, the presence of diabetes, neurological or cardiac disorders, may be responsible for the low efficiency of the treatment of pneumonia, manifested by stagnation or aggravation of symptoms. Smoking patients may develop bronchial hyperreactivity manifested by persistent cough lasting several weeks or months.

In the case of patients who do not show a good response to treatment or their condition deteriorates under treatment, 2 causes of failure should be considered:

a) *Incorrect diagnosis*: heart failure, embolism, cancer, benign tumor, hematoma.

b) Correct diagnosis, but with the occurrence / coexistence of various interferences:

- *Host factors:* local factors (obstruction, foreign body); inadequate immune response; superinfection, empiem;
- *Problems related to the anti-infectious treatment*: error of choice; dosage error, way of administration; non-compliance; side effects or interactions;
- *The germ responsible is not sensitive to the antibiotic given*: mycobacteria, fungi, viruses.

Lobular pneumonia can be complicated by the spread of bronchogenic (intrapulmonary) or hematogenous (remote) pathogens in other organs. In the case of bronchogenic dissemination, local expansion processes (abscess, empyema) are formed or multiple bronchopneumonic outbreaks are formed. Secondary hematogenous dissemination is performed septic matastasis: endocarditis, meningitis, arthritis, etc.

Therapeutic and post-therapeutic monitoring

In the case of hospitalized patients, clinical monitoring should be performed daily, and patients treated in the ATI compartment require continuous evaluation. After 48-72 hours the fever should recover; if the fever persists it is recommended the radiological reassessment (preferably CT) of the patient to detect a complication (pleurisy, abscess). Bacteriological examination of sputum should also be repeated if it remains purulent, as well as hemoculture, inflammatory markers and urinary antigen dosing for *Streptococcus pneumoniae* and *Legionalla pneumophila*. Inflammatory markers have different dynamics; VSH reacts most rapidly, followed by leukocyte formula, C-reactive protein and procalcitonin. If the clinical evolution is good, the paraclinical biological investigations are repeated when the patient is discharged. Since radiological changes are more difficult (4-12 weeks), the control radiograph is not performed at discharge, but at 2 months after the normalization of the clinical signs. The expected evolution of pneumonia that

has responded well to treatment is the cure without radiological sequelae; the persistence of abnormalities on the chest radiograph requires further investigation depending on the type of lesions observed and the patient's field.

Prophylaxis

Prophylaxis can be achieved by stimulating the immune system with immunomodulatory products that are of several types: vaccines (influenza and antipneumococcal), vitamin C, bacterial lysates (Luivac, Bronchovaxom), immunostimulatory products (of vegetable or mineral origin). Immunomodulatory products stimulate the lymphocyte system through bacterial extracts, thus inducing local immunity (IgA mediated).

Pneumococcal vaccination. Vaccination aims to prevent CAP, especially severe forms. Vaccination is indicated especially in the categories of patients at high risk, of which are included: persons over 65 years, with pre-existing respiratory conditions, patients with associated comorbidities (cardio-vascular, neurological, ethyl, diabetes mellitus, liver cirrhosis) and people with immunosuppression (chronic kidney disease, HIV infection, transplants, immunosuppressive treatment, asplenism). The effectiveness of this vaccine results from reducing the incidence of systemic infections due to vaccine strains by 83%. Vaccination with Prevenar-13 is done once in a lifetime, while the Pneumo-23 vaccine requires booster at 3-5 years. Both products are conjugate vaccines.

Influenza vaccine reduces by 32-39% the rate of hospitalizations for influenza or pneumonia in uninstitutionalized individuals and at the same time reduces intraspital mortality by 43-63%. **Influenza vaccination** should be performed annually. Vaccine administration is particularly indicated in people $\geq$ 50 years of age, asylum residents, chronic cardio-pulmonary patients (including asthma), those with chronic metabolic diseases (including diabetes), with impaired renal function, those immunosuppressed and / or HIV, children and adolescents (aged 6 months to 18 years), pregnant women in the second or third trimester of pregnancy during the flu season, health professionals.

Bibliography

1. MURRAY & NADEL'S TEXTBOOK OF RESPIRATORY MEDICINE, SIXTH EDITION. 2016. V.Courtney Broaddus, JD.Ernst, JF.Murray,.
2. Kinkade S, Long NA. Acute Bronchitis. 2016;
3. Llor C, Bjerrum L. Expert Review of Anti-infective Therapy Antibiotic prescribing for acute bronchitis. Expert Rev Anti Infect Ther [Internet]. 2016;14(7):633–42. Available from: http://dx.doi.org/10.1080/14787210.2016.1193435
4. Kazama I, Nakajima T. Acute Bronchitis Caused by Bordetella Pertussis Possibly Co-Infected with Mycoplasma. 2019;60–4.
5. V.Tudorache. Curs de pneumologie. Ed Mirton, Timişoara. 2012;
6. Mejza F, Gnatiuc L, Buist AS, Vollmer WM, Lamprecht B, Obaseki DO, et al. Prevalence and burden of chronic bronchitis symptoms : results from the BOLD study. Available from: http://dx.doi.org/10.1183/13993003.006212017
7. Mejza F, Mastalerz-migas A, Doniec Z, Skucha W. Coexistence of Chronic Bronchitis in Chronic Obstructive Lung Disease. 2018;
8. Palange P, Rohde G. Respiratory Medicine.
9. Lanks CW. C o m m u n i t y - a c q u i red P n e u m o n i a an d H o s p i t a l - a c q u i red Pn e u m o n i a. Med Clin NA [Internet]. 2019; Available from: https://doi.org/10.1016/j.mcna.2018.12.008
10. Kaysin A, Viera AJ, Carolina N, Hill C, Carolina N. Community-Acquired Pneumonia in Adults: Diagnosis and Management. 2016;
11. Karakioulaki M, Stolz D. Biomarkers in Pneumonia — Beyond Procalcitonin. 2019;1–18.
12. Joseph L. Pulmonary and critical care medicine. 2017.

8. PULMONARY ABCESS

1. DEFINITION

Pulmonary abscess is a microbial infection of the lung perenchyma defined as a cavity that contains purulent material and which after drainage of the pus through a bronchial fistula has a hydro-aerial level.

Necrotizing pneumonia is characterized by multiple, small-sized abscesses. Also, pulmonary abscess must be differentiated from septic pulmonary embolisms that have multiple bilateral cavities, often involving the lower lobe and are secondary to endovascular infections.

2. EPIDEMIOLOGY

Pulmonary abscess is a serious respiratory tract infection that without antibiotic treatment results in mortality in about one third of cases. The mortality rate due to pulmonary abscess has been reduced considerably (approx. 10%) due to the use of antibiotics for respiratory infections treatment.

3. ETIOPATHOGENESIS. RISK FACTORS

The source of infection may be endogenous (oropharyngeal, colonic) or exogenous (externally).

The pathways for the entry of infectious agents into the lungs are represented by: the airway through inhalation of infected aerosols or by micro-aspiration from the nasal or oropharyngeal cavity; the hematogenous pathway in the disseminations from infectious outbreaks located at a distance; by contiguity from the neighborhood suppurations (subdiaphragmatic or mediastinal) and by efraction in the case of open chest injuries, trauma.

Risk factors for developing lung abscesses are male (ratio 2: 1), age, alcoholism, dental or periodontal infections, drug use, diabetes, mechanical ventilation, malnutrition, neuromuscular disorders, seizures, mental retardation, treatment with glucocorticoids, cytotoxic or immunosuppressants, immunodepression, gastro-esophageal reflux, decreased cough reflex, bronchial obstruction, sepsis.

Pulmonary abscess can be *primitive* and *secondary*.

a. *Primitive pulmonary abscess*, when the suppurative infectious process develops into an apparently healthy parenchyma previously. The infection pathway is most commonly aerial, by micro-aspiration, and the suppuration is determined by the saprophytic microbial flora from the airways that becomes pathogenic in the presence of favorable risk factors.

b. Secondary pulmonary abscess:

- *of pulmonary origin* involves the over-infection of pre-existing pulmonary parenchymal lesions (pneumonia, bronchial obstruction due to pulmonary neoplasm, enlarged lymph nodes or foreign bodies, pulmonary infarction, silicosis) or the over-infection of pre-existing pulmonary cavities (hydatid cyst, emphysema bubble, bronchiectasis, pulmonary seizure).
- *of extrapulmonary origin* can be determined by hematogenous dissemination during septic conditions (abdominal sepsis, infectious endocarditis, septic thromboembolism); direct propagation from subdiaphragmatic or mediastinal suppurations (subphrenic abscess, broncho-esophageal fistula) or by efraction in the case of open chest wounds.

4. ETIOLOGY

Unlike most other respiratory infections that are caused by single pathogens, pulmonary abscesses are most often caused by mixed populations of bacteria.

The microorganisms most commonly involved in the development of pulmonary abscesses are anaerobic bacteria (*Bacteroides, Fusobacterium, Peptostreptococcus, Veilonella, Prevotella*), followed by species from the *Streptococcus group* (especially the *Streptococcus milleri group*).

Of the aerobic or facultative anaerobic bacteria isolated in pulmonary abscesses, we mention: *Staphylococcus aureus* (including MRSA), *Streptococcus spp., Klebsiella pneumonie, Pseudomonas aeruginosa, Haemophilus parainfluenza, Acinetobacter spp., Escinetobacter spp., Nocardia, Escherella sp.* Pulmonary abscess may also be associated with mycobacteria, fungi and parasites (*Paragonimus, Entamoeba* and *Echinococcus*).

A recent study in Taiwan reported *Klebsiella pneumonia* as the most common pathological agent involved in the development of pulmonary abscesses. Thus, we can say that the bacterial etiology of pulmonary abscess is not yet fully understood and is constantly changing.

5. PATHOLOGY

Three phases are described in the evolution of pulmonary abscess:

a. *The constitutive phase* (pneumonic) in which fibrin-leukocyte alveolitis transforms into suppurative alveolitis;

b. *The vomiting phase* (recent abscess) in which the cavity with purulent content is formed, which is subsequently evacuated by bronchial route;

c. *The open focal phase* (chronic suppuration) in which a pulmonary cavity persists, with variable fluid level and communicating with the bronchi.

6. CLINICAL FEATURES

In the *onset phase* the signs and symptoms of pulmonary abscess cannot be differentiated from those of a pneumonia, in the case of aerobic infections, the onset *being acute* with fever, cough with muco-purulent expectoration, chest pain, asthenia, anorexia, sometimes hemoptysis. In the case of anaerobic infections, the onset is *insidious*, the clinical manifestations extend for a longer period (between 2 weeks and 3 months, or longer). Subsequent evolution is characterized by the persistence of fever, the septic state and the aggravation of the general state, specific to the stage of the abscess.

The suppuration (opening) phase of the abscess is marked by the amplification of coughing accesses with abundant expectoration, sometimes vomiting. Sputum is muco-purulent, purulent or bloody pus, stratified and odorous (fetid odor). The fever disappears with the evacuation of the purulent collection. In case of persistence infectious process, the patients present with purulent sputum (100-300 ml/24h), pallor, oscillating type fever, weight loss, anemia, symptoms specific to the bronchial drainage stage. If the pulmonary abscess becomes chronic, digital hypocracy, cachexia and respiratory failure may occur over time.

Physical signs are not specific to pulmonary abscess. The diagnosis may be suggested by the presence of favorable factors such as poor dental hygiene, alcohol and drug use, affected patient. Also, fetid halitosis may be an indication for pulmonary abscess. Submatitis, bronchial rales and pleural friction may be present.

7. PARACLINICAL EXPLORATIONS

Radiologic examination plays an important role in diagnosing lung abscess. In the constitution phase the *chest x-ray* may reveal one or more homogeneous opacities, with blurred contour and localization predominantly in the posterior segments. In the suppuration phase, after communication with the bronchial shaft and after vomiting, a cavity image with intrapulmonary hydro-aerial level appears, with the large vertical axis. Pulmonary abscesses are most commonly located in the posterior segment of the right upper lobe or in the apical segment of the lower lobe of both lungs. Chest radiography in two incidences (posterior-anterior and lateral) helps to locate the lung abscess more precisely. Also, the x-ray may show pleural effusion or hydropneumothorax (bronchopulmonary fistula).

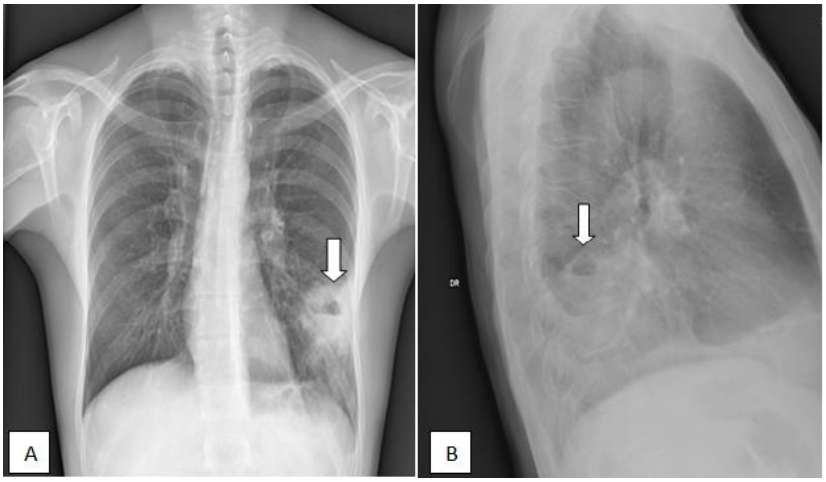


Fig. 1: A - patient aged 65 years, chest radiograph posterior-anterior incidence - cavity image with thick wall and horizontal hydro-aerial level projected left basal; B - patient aged 60, chest radiograph lateral incidence - opacity with hydro-aerial level projected at the apical region of the lower right lobe. Note: white arrow ( ) - opacity with hydro-aerial level.

Chest tomography is sometimes required in unclear diagnostic cases for more precise delimitation of lesions and to differentiate abscess from other lung conditions.

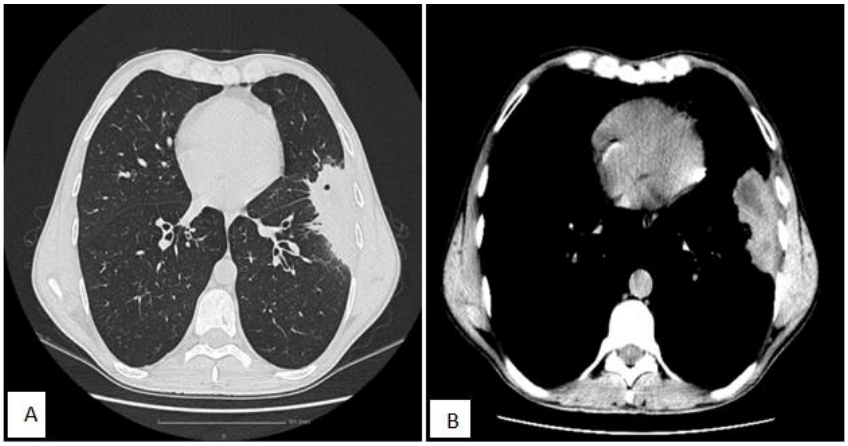


Fig. 2: Chest computed tomography. Patient 69 years old. A - axial section in the window of visualization of the pulmonary parenchyma: condensation process at the anterior segment, left inferior lobe, with micro-aeration; B - axial section in the medastinal window: pneumonic process abscessed with central hypodense areas of necrosis.

The laboratory examination shows leukocytosis with neutrophils, accelerated VSH, increase of acute phase reactants and sometimes anemia. The sputum examination reveals the presence of altered leukocytes (piocytes), and in the case of secondary suppurations, it reveals etiological elements to the primary pulmonary pathology (hydatic "hooks", neoplastic cells, micelles).

It is recommended to identify pathogens by bacteriological examination of sputum. This is often difficult to achieve in practice because anaerobic bacteria require special cultivation conditions, and the polymorphic flora highlighted only partially reflects the flora in the suppurative process due to contamination of the upper airways. When possible, hemocultures, sputum cultures and pleural fluid cultures are recommended.

Bronchoscopy is part of the diagnostic arsenal of pulmonary abscess, being useful for the exclusion of a bronchial obstruction of a tumorous nature or by the presence of a foreign body, in this case also having a therapeutic role. Also, by analyzing the bronchial aspirate a mycobacterial infection can be excluded.

Transthoracic or transesophageal aspiration are methods of collecting less used bacteriological examination samples, being reserved for cases that do not respond to empirically administered antibiotic treatment.

8. POSITIVE DIAGNOSIS

The positive diagnosis is supported by the presence of clinical symptomatology, biological changes, the presence of the hydro-aerial image on the chest radiograph and the identification of some favorable factors. It is necessary to identify pathogens (bacteria, fungi, parasites) as well as the nature of the lung abscess (primitive or secondary).

9. DIFFERENTIAL DIAGNOSIS

The differential diagnosis depends on the stage in which we examine the patient. Thus, in the constitution phase the pulmonary abscess must be differentiated from the conditions that cause pneumonic opacities (pneumonia, eosinophilic infiltrate, lung tumors).

In the open suppuration phase, the differential diagnosis is made with the excavated bronchopulmonary neoplasm (smoking history, radiological cavern "in the border" with thick walls), excavated cavity pulmonary tuberculosis (positive sputum BK), hydatid cyst superinfected, pulmonary infarction, blisters superinfected, bronchiectasis, hydropneumothorax, closed empyema, pulmonary hematoma, pulmonary seizure, mycorrhizal fungal cavities, diaphragmatic hernia, etc. In the chronic suppuration phase the cavern and tuberculous fibrosis, the excavated silicotic nodule, the Wegener granulomatosis should be excluded.

10. EVOLUTION AND PROGNOSTICS

With the introduction of antibiotic treatment, the evolution and prognosis of this disease have changed. The correct administration of the treatment can lead to healing in 75-80% of cases, chronicization in 5% of cases and death in approx. 10% of cases. Healing can be done without sequelae, but it depends on several factors: the cause of the suppuration, the virulence of the germs involved, the resistance of the body, the correct establishment of the diagnosis and the treatment.

Factors for a reserved prognosis of pulmonary abscess are: giant pulmonary abscess (> 6 cm), advanced age, confusional state, neoplasia, malnutrition and bacterial infection with Klebsiella pneumoniae, Pseudomonas aeruginosa or Staphylococcus spp.

Pulmonary abscess can have the following complications: hemoptysis (in the acute phase of suppuration), empyema, purulent pericarditis, mediastinitis, healing with retractable fibrosis, which causes the development of bronchiectasis, the persistence of a residual cavity with fungal grafting, hematogenic septic dissemination (cerebral, liver, renal, suppurated arthritis).

11. PREVENTION

The prophylaxis of developing lung abscess is done by the correct treatment of pulmonary infections and infections in the sphere of otorhinolaryngology, by dental hygiene, by avoiding exhaustion, cold, humidity, exposure in polluted areas and by treatment of underlying diseases (diabetes, alcoholism).

12. TREATMENT

Anti-infectious treatment - antibiotic therapy is the central element of the pulmonary abscess treatment. The initiation of antibiotic treatment should be arranged as soon as possible after the results of the bacteriological examination. As this is not possible most of the time, empirical treatment with broad-spectrum antibiotics is given due to the presence of polymicrobial flora. The optimal duration of administration of the treatment has not been established exactly, usually being maintained for a period of 4-6 weeks.

The standard treatment for anaerobic germ infections is with clindamycin (600 mg i.v/8 h), which has been shown to be superior to penicillin given alone. Some anaerobic bacterial species (*Bacteroides spp., Fusobacterium spp*.) Produce β-lactamases thus becoming resistant to penicillin, the recommendation is to associate with clavulanic acid or metronidazole. Metronidazole alone is associated with a high rate of therapeutic failure.

Any combination of β-lactam/β-lactamase inhibitor (ticarcilin-clavulanate, ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam) is a treatment alternative. Furthermore, carbapenems (imipenem or meropenem), fluoroquinolones (moxifloxacin), chloramphenicol or second-generation cephalosporins (cefoxitin, cefotetan) can be used, their efficacy being comparable to that of ampicillin-sulbactam.

For methicillin-resistant staphylococci (MRSA) it is recommended to take linezolid 600 mg iv/12 h or vancomycin 15 mg/kg body/12 h. Documenting the infection with Actinomyces or Nocardia requires a longer treatment period (6 months). Antibiotic treatment may be ineffective in patients with immunodeficiencies, in the case of infection with *Pseudomonas aeruginosa* or *Staphylococcus aureus*, as well as in large abscesses (> 8 cm).

Therefore, it is recommended to treat pulmonary abscess with broad-spectrum antibiotics, such as Clindamycin (600 mg iv/8 h), then 300 mg po/6 h (as soon as the patient becomes afebrile, with general improved condition) or combination ampicillin / sulbactam (1.5-3 gr. iv/6 h). Alternatively, piperacillin/tazobactam 3.375 gr. iv/6 h or meropenem 1 gr. iv/8am.

An effective response to antibiotic therapy can be observed after 3-4 days, the general condition will improve after 4-7 days, but complete healing with radiographic normalization can be observed after two months. If there is no improvement in general condition or fever persists after 7-14 days of treatment, a bronchoscopy or other diagnostic tests are performed to reevaluate anatomical changes and microbial characteristics.

General measures involve bed rest under hospital conditions, normal-caloric diet (hypercaloric in undernourished patients), hydroelectrolytic rebalancing and respiratory rehabilitation with postural drainage. Drainage procedures include percussion and positioning to increase airway drainage. Symptoms are treated with antipyretics, analgesics, expectorants.

Surgical treatment should be considered in cases of pulmonary abscesses greater than 6 cm in diameter if they do not respond to antibiotic treatment or if the symptoms persist for more than 12 weeks with appropriate therapy, as well as if a non-infectious etiology is suspected. The options for surgery are: drainage of the collection through a chest tube or surgical resection of the lung abscess.

Bibliography

1. Investigations C. The Importance of Obligate Anaerobes and the Streptococcus anginosus Group in Pulmonary Abscess : A Clone Library Analysis Using Bronchoalveolar Lavage Fluid. 2016;8555:80–9.
2. Kuhajda I, Zarogoulidis K, Tsirgogianni K, Tsavlis D, Kosmidis C, Tsakiridis K, et al. Lung abscess-etiology , diagnostic and treatment options. 2015;3(6).
3. Cai X, Yang Y, Li J, Liao IX, Qiu IS, Xu IJ, et al. Logistic regression analysis of clinical and computed tomography features of pulmonary abscesses and risk factors for pulmonary abscess-related empyema. 2019;1–6.
4. MURRAY & NADEL'S TEXTBOOK OF RESPIRATORY MEDICINE, SIXTH EDITION. 2016. V.Courtney Broaddus, JD.Ernst, JF.Murray,.
5. Gabriel U, Adrian C. Terapeutică medicală. Ed Polirom. 2014;
6. Bo PL. Ampicillin + sulbactam vs . clindamycin ± cephalosporin for the treatment of aspiration pneumonia and primary lung abscess. 2004;
7. Hooper C, Maskell N. PLEURAL INFECTION AND LUNG ABSCESS. :186–90.
8. Duncan C, Nadolski GJ, Gade T, Hunt S, Hunt S. Understanding the Lung Abscess Microbiome : Outcomes of Percutaneous Lung Parenchymal Abscess Drainage with Microbiologic Correlation. 2017;
9. Magda P. Curs de radiologie și imagistică medicală. UMF Timișoara. 2008;
10. Gadkowski LB, Stout JE. Cavitary Pulmonary Disease. 2008;21(2):305–33.
11. Takayanagi N, Kagiyama N, Ishiguro T, Tokunaga D. Etiology and Outcome of Community-Acquired Lung Abscess. 2010;0105:98–105.
12. Wang J, Chen K, Fang C, Hsueh P, Yang P, Chang S. Changing Bacteriology of Adult Community-Acquired Lung Abscess in Taiwan : Klebsiella pneumoniae versus Anaerobes. 2005;100(February):915–22.
13. V.Tudorache. Curs de pneumologie. Ed Mirton, Timișoara. 2012;
14. Nicolini A, Cilloniz C, Senarega R, Ferraioli G, Barlascini C. Lung abscess due to Streptococcus pneumoniae : a case series and brief review of the literature.
15. Dan L. L, Anthony S. F, Dennis L. K, Stephen L. H, J. Larry J, Joseph L. Harrison - Medicină internă. Ediția a 18-a. 2014.

9. CYSTIC ECHINOCOCCOSIS

1. DEFINITION

Hydatic cystic disease or *echinococcosis* is a parasitosis caused by infection with the larval stage (metacestode) of *Echinococcus* tapeworm.

Three forms of echinococcosis are known in humans: *cystic, alveolar and polycystic*.

2. ETIOLOGY

Four species of *Echinococcus* tapeworm are known to cause disease in humans. *Echinococcus granulosus* causes cystic hydatidosis; *Echinococcus multilocularis* causes alveolar echinococcosis, and polycystic disease is determined by *Echinococcus vogeli* and *Echinococcus oligarthus*.

The most common species responsible for human echinococcosis is *E. granulosus*, followed by *E. multilocularis*, the latter being usually more pathogenic. Polycystic hydatidosis is rarely encountered.

3. EPIDEMIOLOGY

Hydatic cystic disease remains an important cause of morbidity in humans in endemic areas. The infection is found mainly in the areas where shepherding is practiced and where dogs are used to lead the sheep.

E. granulosus is widespread on all continents, with a higher prevalence of the infection being found in the Mediterranean basin, especially in Italy, Spain, Albania and the countries of the former Yugoslavia. The infection is also found in Central and South America, sub-Saharan Africa, China, Russia and the countries of the former Soviet Union.

E. multilocularis is found in the alpine, sub-Arctic or Arctic regions, being endemic in Canada, areas of the United States, Central and Northern Europe, China and northern Japan.

E. vogeli and *E. oligarthrus* are endemic only in Central and South America.

4. PATHOGENESIS AND RISK FACTORS

E. granulosus is a broad worm of the Cestods class, whose life cycle requires two hosts: a definitive host, usually the dog or other canids and an intermediate host represented by sheep, cattle, pigs, goats and other mammals, as well as by human. The adult worm is 3-7 mm long and is located in the small intestine of the definitive host, consisting of 3-5 proglotids. Infected dogs eliminates tapeworm eggs through faeces, thus contaminating soil and vegetation. These eggs can remain viable for a long time in the environment. Intermediate hosts (sheep are the main intermediary hosts), along with humans, are also infected by ingesting viable eggs of E. granulosus. The human acquires the disease by consuming water or contaminated raw vegetables, as well as by direct contact with infected dogs. Once they reach the intestine of the intermediate host, the parasite eggs release embryos (oncospheres). Oncospheres penetrate the intestinal mucosa, after which they are transported through the blood and lymphatic system most often to the liver and lungs, but other organs can be involved (heart, brain, bone, kidney, muscle). At the organ level in which it is fixed, it develops forming unilocular hydatid cysts with liquid content. Echinococcus larvae develop in these cysts. The cysts have three layers: outer membrane (pericyst), middle membrane (ectocyst) and inner germinal layer (endocyst / proligerous membrane), from which secondary cystic formations (daughter cysts) develop.

Within these daughter cysts, a large number of larvae or protoscoleces develop. The life cycle of the parasite becomes complete when the definitive host (dog) ingests meat / organs containing cysts from the intermediate host. Once inside the definitive host, the protoscoleces evaginate and attach themselves to the intestinal mucosa, subsequently developing the mature parasite in a period of 4-7 weeks. The human does not transmit the disease further, thus representing a dead end in the life cycle of the parasite.

The incubation period of human hydatidosis is variable, usually lasting several years. The growth rate of hydatid cysts is slow and varies depending on the affected organ. Cysts with pulmonary localization have a continuous growth of 1-5 cm / year.

Risk factors for perpetuating hydatidosis are poor hygiene, low socio-economic status, contact with infected dogs and feeding them with debris from contaminated animals, as well as lack of disease control programs.

5. CLINICAL FEATURES

The hydatid cyst is often presented as a solitary cyst, most commonly located in the liver (50-70% of cases) or lungs (20-40%); in 10-15% of the cases other organs are involved.

Pulmonary echinococcosis has no specific symptomatology. Clinical manifestations vary depending on the size and condition of the cyst (intact or broken). Most patients are asymptomatic for a good period of time, and the disease is usually discovered incidentally following a chest x-ray. The onset of symptomatology is most often the consequence of cyst rupture or due to the compressive effects of a large cyst.

Symptoms of pulmonary echinococcosis are coughing with/or without expectoration, chest pain, progressive dyspnea, small hemoptysis and low-grade fever.

The pulmonary hydatid cyst may rupture spontaneously or during surgical treatment, its contents being discharged into the bronchial tree, pleural or peritoneum. The rupture of the cyst in the airways determines the externalization of the contents by expectorating a large amount of clear liquid, with a salty taste and which may contain fragments of the proligerous membrane (hydatic vomiting), the appearance of cough and fever. The broken cysts can be infected with bacteria and / or fungi, the evolution being towards abscess.

Moreover, the broken hydatid cyst may be associated with a hypersensitivity response, manifested by hives, edema, sometimes even anaphylactic shock (rare). The rupture of a cyst in the pleura can lead to the appearance of a pleural effusion, empyema or pneumothorax. Cyst rupture in the peritoneum causes peritonitis.

Intact cysts, large in size, can erode into adjacent structures causing bone pain, bleeding or limiting airflow through airway compression.

6. POSITIVE DIAGNOSIS

The diagnosis of pulmonary echinococcosis is established using imaging investigations, serological and microscopic tests.

X-ray and *chest CT* are the most commonly used imaging tests to establish the diagnosis. On chest radiography, the uncomplicated (closed) hydatid cyst has an aspect of homogeneous, round or oval opacity, with the diameter from 1 to 20 cm, subcostal intensity, clearly delimited contour and adjacent normal lung tissue. The location of the hydatid cyst is predilected in the lower lobes.

The complicated hydatic cyst can have several radiological aspects: hypertransparency at the upper pole of the opacity in the form of a crescent (it signals the imminence of the rupture),

given by the penetration of the air between the pericyst and the proligerous membrane, secondary to a crack produced at the level of the cyst's adventitia; the sign "lily flower" (pathognomonic) appears in the case of a partial cyst evacuated from the liquid content. This sign is formed when the air enters the cyst and determines the detachment of the endocyst from the pericyst, thus the endocyst floats in the fluid from the partially evacuated cyst.

Chest tomography allows differentiation of the hydatid cyst from other pulmonary cyst images (benign or malignant tumors, abscesses of other etiology). Highlighting daughter cysts within the large cyst when examining CT is pathognomonic to hydatidosis.

Serological tests are based on ELISA-like reactions to detect IgG antibodies, indirect hemagglutination or indirect immunoflorescence. The sensitivity of serological tests for pulmonary hydatid cysts is lower compared to liver localization. Also these tests can be positive for other parasitic infections (helminths). The results of serological tests should be interpreted in the context of clinical and imaging signs. Therefore, a negative serological test does not exclude the diagnosis of echinococcosis.

Parasitological examination with protoscoleces highlighting can be performed from sputum or pleural fluid in case of a broken cyst.

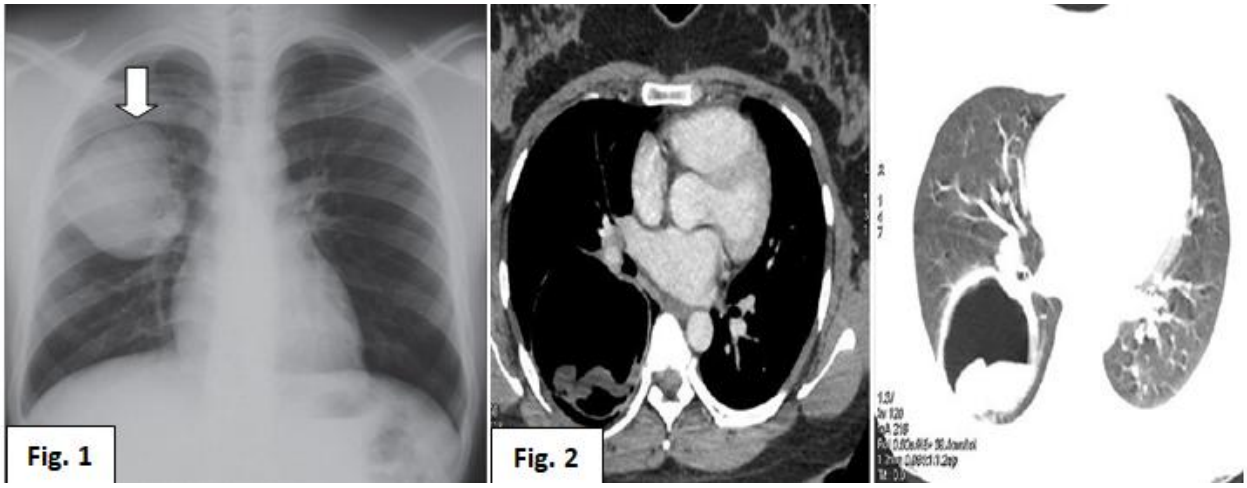


Figure 1: Pulmonary hydatid cyst at the level of the right upper lobe - homogeneous, oval, subcostal intensity, clearly delimited (white arrow). (1) Figure 2: CT chest mediastinum and lung window - highlights a cystic formation in the lower right lobe that contains floating endochistic membranes (the sign of "lily flower"). (2)

7. DIFFERENTIAL DIAGNOSIS

The hydatid cyst must be differentiated from benign or malignant pulmonary tumors, cavity tuberculosis, pulmonary abscess, pulmonary metastases and airway cyst.

8. TREATMENT

The first choice treatment of the hydatic cyst is the *surgical* one, in the case of patients who can tolerate the procedure. *Drug treatment* plays an important role in the therapeutic behavior, usually being associated with the surgical one.

Surgical treatment has the following objectives: complete removal of the cyst with removal of the endocyst; avoiding contamination and spillage of liquid content; management of residual cavity and preservation of adjacent lung parenchyma. Both preoperatively (1-3 months)

and postoperatively (6 months), antiparasitic chemotherapy (albendazole) is recommended to prevent relapse. In the case of cyst rupture during surgery, praziquantel may also be given, as it has a scoliotic effect.

Antiparasitic chemotherapy is indicated in patients with small hydatid cysts (<5 cm) and patients who have contraindications for surgical treatment: patient refusal, presence of multiple organ infections, multiple or recurrent cysts and complicated cysts. Albendazole is currently the drug of choice, at a dose of 10-15 mg/kg/day, for a period of 6 months, given in 28-day cures, separated by 14 days off. The combination of praziquantel at a dose of 25 mg/kg/day, 7 days/ cycle, increases the effectiveness of the drug treatment.

Under proper treatment, the evolution of the disease is generally favorable.

9. PREVENTION MEASURES

Echinococcosis can be prevented in endemic areas by improving hygiene conditions, by washing fruits and vegetables, by limiting the access of dogs to infected animals, by reducing the number of stray dogs, by administering praziquantel to infected dogs or by vaccinating sheep. Vaccination of animals to prevent echinococcosis is an important goal in disease management.

Bibliography

1. Wahlers K, Menezes CN, Wong ML, Zeyhle E, Ahmed ME, Ocaido M, et al. Cystic echinococcosis in sub-Saharan Africa. Lancet Infect Dis [Internet]. 2012;12(11):871–80. Available from: http://dx.doi.org/10.1016/S1473-3099(12)70155-X
2. Sarkar M, Pathania R, Jhobta A, Thakur BR, Chopra R. Cystic pulmonary hydatidosis. 2016;179–91.
3. WHO / OIE Manual on Echinococcosis in Humans and Animals : a Public Health Problem of Global Concern Edited by.
4. MURRAY & NADEL'S TEXTBOOK OF RESPIRATORY MEDICINE, SIXTH EDITION. 2016. V.Courtney Broaddus, JD.Ernst, JF.Murray,.
5. Argemi X, Santelmo N, Lefebvre N. Images in Clinical Tropical Medicine Pulmonary Cystic Echinococcosis. 2017;97(3):641–2.
6. Simon D, Koegelenberg CFN, Sinha S, Allwood BW, Irusen EM. Can Large Hydatid Cysts Resolve with Medical Treatment Alone ? 2016;8000:428–31.
7. V.Tudorache. Curs de pneumologie. Ed Mirton, Timişoara. 2012;
8. Mifsud S, Schembri EL, Gauci J, Mizzi A, Azzopardi CM, Micallef J. Reminder of important clinical lesson The non-resolving lung cavity : a case of pulmonary cystic echinococcosis. 2017;1–5.
9. Thapa B, Sapkota R, Kim M, Barnett SA, Sayami P. Surgery for parasitic lung infestations : roles in diagnosis and treatment. 2018;10(Suppl 28):3446–57.
10. Embleton DB. Evaluation of Patients with Cystic Echinococcosis Kistik Ekinokokkozis Olgularının Değerlendirilmesi. 2017;(March 2016):25–9.
11. Dudha M, Shaikh Z, Bhaiyat M, Bhaiyat Z, Wadiwala IJ. Respiratory Medicine Case Reports Case Report A Case of Echinococcal Cyst of the Lung. Respir Med Case Reports [Internet]. 2018;25(October):286–92. Available from: https://doi.org/10.1016/j.rmcr.2018.10.007

10. BRONCHIECTASIS

Definition
Bronchiectasis is defined as a permanent and progressive dilatation of one or more medium-sized bronchi (subsegmentation). In this process are involved the infection, inflammation, and vicious repair of the bronchial mucosa, which causes lesions in the muco-ciliary apparatus with the subsequent destruction of the bronchial wall.

Epidemiology
The exact prevalence of non-cystic fibrosis (NCFB) bronchiectasis is not known. Increased awareness of the disease, as well as the increasing use of high-resolution computed tomography (HRCT) , have led to an increase in the diagnosis rate and thus the prevalence of the disease.

Pathology
The most accepted mechanism for the onset and development of NCFB has been described by Cole, in which infection, airway inflammation and lung injury make up a "vicious circle". Affecting mucociliary clearance creates optimal conditions for the accumulation of secretions and their stasis, inducing the recruitment of neutrophils and other inflammatory cells, which in turn will release cytokines / chemokines, proteases and antimicrobial peptides. These are combined by further stimulating mucus secretion, decreasing bactericidal capacity, initiating bronchial remodeling and further altering ciliary function; thus constituting the substrate for colonization and subsequent infection, which in turn will "close the circle" by secondary exacerbation of inflammation. Airway lumen inflammation is predominantly mediated by neutrophils, which secrete elastase and myeloperoxidase, pro-inflammatory cytokines CXCL-8 (IL-8), TNF-a, IL-1b and leukotriene B4.
From the histological point of view, the bronchial dilation can be observed with thickened bronchial walls, with edema, inflammation, mucoid impact and neovascularization. Peribronchiectatic phenomena of destruction of the interstices and alveoli, fibrosis, emphysema occur.

Etiology
The etiology of bronchiectasis recognizes a multitude of factors. The main agents involved in the etiology of NCFB are presented in table no.1.

Table no. 1

Etiological categories	Examples
Idiopathic (32-66%)	-
Infections (20-40%)	Bacterial (eg Pseudomonas, Staphilococcus, Haemophilus) Mycobacteria (tuberculous and non-tuberculous) Viral (adenovirus, influenza, measles virus)
Immunodeficiencies (5%)	*Primary:* hypogamaglobulinemia (including IgG subclass deficiency), chronic granulomatous disease, complement deficiencies *Secondary:* HIV, immunosuppressive treatments
Bronchial obstruction	Extrinsec compression (lymph nodes, tumor) Inhaled or intrinsic foreign body (broncholithiasis) Neoplasm (endobronchial injury) Mucoid impact (allergic bronchopulmonary aspergillosis) Postoperatory
Diseases of connective tissue (connectivity) (1-10%)	Rheumatoid arthritis, systemic lupus erythematosus, sdr. Sjögren, relapsing polychondritis, inflammatory bowel disease
Congenital diseases or structural defects (except cystic fibrosis) (1-2%)	Deficiency of α1-antitrypsin Defects of the cilia (SD Kartagener), primary ciliary dyskinesia Sdr. yellow nails, congenital bronchial cartilage deficiency, congenital trheobronchomegaly (Mounier-Kuhn sdr.)
Inhalation of toxic substances	Ammonia, chlorine, NO2
Various	Associated COPD, allergic bronchopulmonary aspergillosis, traction bronchiectasis (in interstitial diseases), post-transplant

Clinical manifestations

Clinical symptoms are suggestive and highly variable, usually increased during infectious acute outbreaks.

Cough is chronic with muco-purulent expectoration in over 95% of cases. From the quantitative point of view, the sputum has a variable abundance, being able to transform into bronchorrhea during exacerbations. In case of infections with anaerobic germs, sputum stench also occurs.

Hemoptysis, of variable abundance, is described in almost 50% of patients, also representing an increased severity factor.

Dyspnea and fatigue are present in the clinical picture in a very high proportion.

Common in patients with bronchiectasis is *chronic sinusitis*, manifested by intermittent excretion of nasal secretions, until severe purulent emission.

Digital hypocracy can occur in the late stages of chronic illness.

Crackles (up to 73% of patients), rhonchi (44%) and wheezing (21-34%) are the main signs found on physical lung examination.

Although most of the time the symptoms are suggestive and consistent, there are also asymptomatic cases, establishing the presence of bronchiectasis by HRCT .
An exacerbation is suspected in a person with bronchiectasis, when there is an aggravation / increase in intensity, during 48 hours, of at least 3 of the symptoms: cough, increased volume and / or consistency of expectoration, sputum purulence, dyspnea, decreased tolerance to effort, fatigue, hemoptysis, influenced general condition.

Paraclinical investigations

Laboratory: hemoleucogram, HIV serology, electrophoresis, VSH, CRP, α1-antitrypsin, FR, antibodies A, B for Sjögren's syndrome, cyclic citrulline peptide for scleroderma etc.
Bacteriology: sputum (Gram stain) and 3 Ziehl–Nielsen stain samples + cultures, molecular tests (GeneXpert for BK).
Sputum cultures should be obtained in all patients with bronchiectasis. The most common organisms initially isolated from sputum from patients with NCFB are gram-negative bacteria, including Haemophilus influenzae (47%), Ps. aeruginosa (12%) and Moraxella catarrhalis (8%). In time, the bacteriological distribution changes, Ps. Aeruginosa increasing in frequency. New methods (molecular techniques) for studying the lung microbioma have found that the diversity of airway infection is underestimated, anaerobic bacteria are found in up to 83% of sputum samples, and that three taxonomic entities: Streptococcaceae, Pseudomonadaceae and Pasteurellaceae appear to be dominant. Colonization with Ps. aeruginosa defines a special clinical phenotype of bronchiectasis, associated with a 3-fold increase in the risk of death, an almost 7-fold increase in the risk of hospitalization, as well as worsening quality of life and more frequent exacerbations.
Radiology. Standard chest radiography has a moderate sensitivity (88%) and a somewhat poor specificity (74%) for detecting bronchiectasis. However, moderate-severe NCFB may be reflected on the X-ray as accentuated, deformed pulmonary drawing, thickened bronchial walls, "tram tracks", cystic shadows with liquid level, ring opacities or even normal image.
From an imaging point of view, bronchiectasis is most easily identified by HRCT of the chest, which is currently considered as the gold standard in diagnosing / confirming bronchiectasis, having a sensitivity of 96% and a specificity of 93%. At any level, the diameter of the bronchi must be larger than the adjacent blood vessel (broncho-arterial ratio> 1); the broncho-arterial ratio increases with age and smoking. Other imaging features that may accompany NCFB include thickening of the bronchial wall, mucoid impact, "tree in bud" appearance, captive air areas (appearing more transparent), mosaicism and emphysema.
The classic classification of bronchiectasis includes: cylindrical (tubular), varicose (moniliform) and sacular (cystic), with a later correspondence with the clinical expression:
cylindrical forms - mild clinical manifestations, varicose forms - moderately-severe clinical manifestations, cystic forms - severe clinical manifestations.

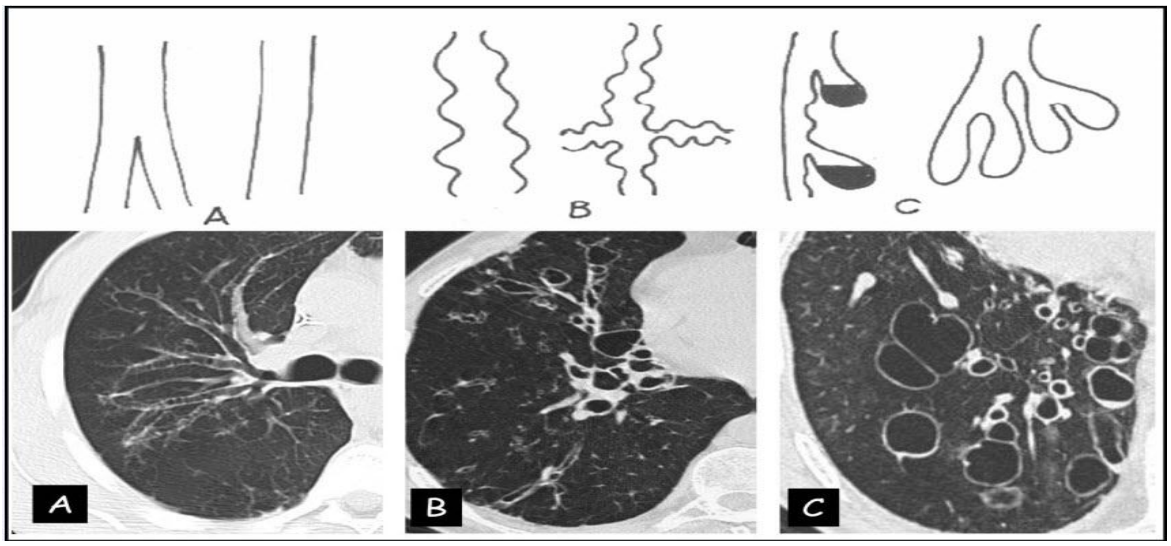


Figure 1. Clasification of bronchiectasis: A – Cylindrical, B – Varicose, C – Saccular

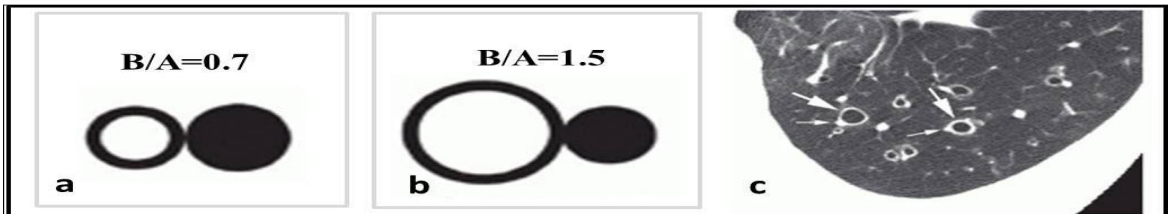


Figure 2. Bronchovascular axis: A – subunitary ratio (normal), B – supraunitary ratio in favor of bronchus (bronchiectasis), C - characteristic CT features (small white arrow shows vessels, big white arrow shows bronchus)

Respiratory functional explorations. Patients with NCFB may have obstructive, restrictive ventilatory dysfunction or relatively normal spirometry values. There is a clear relationship between FEV1 and prognosis, as obstruction that tends to become severe (FEV1 <50%) is associated with a history of infection or colonization with Pseudomonas, multi-lobular spread of the disease, a larger sputum volume, with a more purulent, and these patients have at least four exacerbations over a 2-year period.

Positive diagnosis

The bronchiectatic disease implies both the permanent dilation of the bronchi observable on the radiological evaluation by HRCT, as well as the presence of a characteristic symptomatology: chronic cough, most often (70%) with abundant sputum and repeated exacerbations. Most patients with bronchiectasis have clinical symptoms of variable intensity, more pronounced during the acute exacerbations induced by different infections.

Differential diagnosis

It is done with chronic bronchitis, tuberculosis, pulmonary abscess, COPD, asthma, cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA). Immunodeficiencies manifest with recurrent infections, but not always bronchiectasis are present. For this reason, the clinical and radiological data are insufficient for their differentiation of bronchiectasis, further examinations

becoming necessary for an etiological diagnosis. In all cases, it is necessary to examine sputum and additional cultures for mycobacteria and fungi, functional explorations (asthma / COPD detection), sweat test, etc.

Particular clinical situations

In more than 50% of cases the etiology of bronchiectasis is represented by the obstructive and infectious syndromes, thus detaching some particular phenotypes: BCOS (Bronchiectasis - COPD Syndrome), bronchiectasis and asthma, post-tuberculosis bronchiectasis and non-tuberculosis mycobacteriosis, Cystic Fibrosis.

Severe prognostic factors are:

• *Bacteriological:* colonization with Ps. aeruginosa, MRSA, or a high bacterial load;
• *Radiological:* bronchiectasis extended on> 3 lobes, cystic forms, thickening of the bronchial walls, high mucoid impact, mosaicism, emphysema;
• *Functional:* obstructive ventilatory dysfunction, rapid decline of FEV1, increased residual volume / total lung capacity ratio, reduced carbon monoxide transfer factor;
• *Effort / dyspnea capacity:* MRC dyspnea score 4-5;
• *Symptomatology:* sputum volume> 25 ml / day, purulent and stable sputum, severe cough;
• *Etiology:* bronchiectasis associated with COPD, with rheumatoid arthritis, inflammatory bowel disease, connectivity, asthma and immunodeficiencies;
• *Exacerbations:* ≥ 3 / year, severe exacerbations requiring hospitalization;
• *Comorbidities:* metastatic or haematological cancers, COPD, cognitive impairment, inflammatory bowel disease.

The severity of bronchiectasis is assessed by multidimensional evaluation using scales, of which the most used are BSI (Bronchiectasis severity index), BACI (Bronchiectasis Aetiology Comorbidity Index), FACED.

The nature, prevalence and impact of comorbidities on disease severity and mortality prediction were captured in the BACI questionnaire. These questionnaires can guide the monitoring and personalized treatment of these patients.

Evolution

The evolutionary path of the NCFB is highly variable. Mild disease is characterized by the absence of bacterial colonization, rare exacerbations, reduced radiological extension and fewer symptoms. While severe forms include colonization with Ps. aeruginosa, frequent and severe exacerbations, intense dyspnoea (MRC 3-4), with impaired lung function and radiological extension on more than 3 lobes (quantification is done through the scales listed above).

Complications

Infectious complications can be of a type of permanent bronchial infection, peribronchiectatic pneumonia / pulmonary abscess, pleural empyema or distant septic dissemination. Exacerbations negatively affect the quality of life of patients, the results of long-term treatment, also representing a major factor in the healthcare costs associated with bronchiectasis.

Hemorrhagic complications are most often triggered by an infectious exacerbation, sometimes life-threatening.

Chronic respiratory failure develops over many years culminating in chronic lung failure.

Amyloidosis appears as a side effect of chronic suppuration and is suggested by the existence of digital hypocracy, the establishment of a nephrotic syndrome and possibly a hepato-splenomegaly.

Treatment

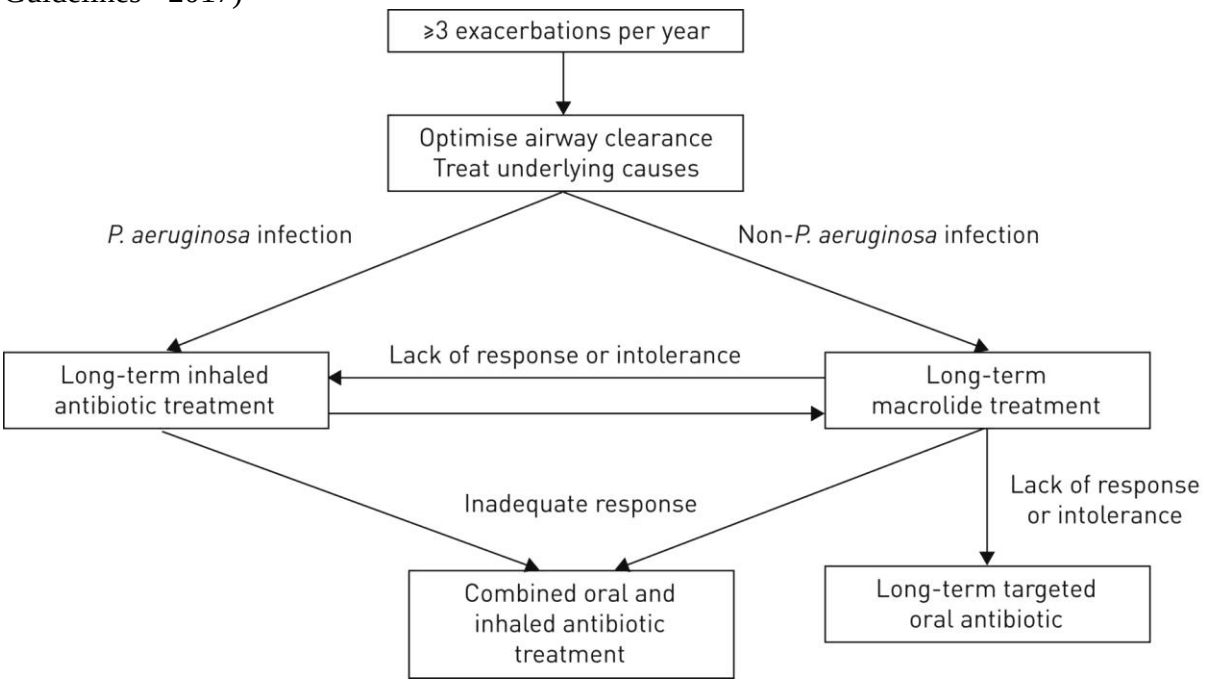
The management in bronchiectatic disease aims to reduce symptoms, improve quality of life, reduce the rate of exacerbations and reduce the risk of further complications such as severe exacerbations, chronic bacterial colonization and decline in lung function. For this, several aspects will be followed stepwise and systematically:

Elimination of the causal agent. Anamnesis and an extremely rigorous etiological investigation are very important, as the effectiveness of the treatment can be greatly influenced if a treatable cause is discovered.

Improving mucociliary clearance and facilitating bronchial drainage is the fundamental intervention. Excessive volume and increased viscosity of the mucus can be alleviated by inhalation of hyperosmolar agents, physiotherapy techniques, and the use of bronchial dislocation devices. Pulmonary rehabilitation programs increase the quality of life, effort tolerance and time duration until the next exacerbation.

Infection Control / Exacerbation. Acute exacerbations of bronchiectasis should be treated promptly with broad-spectrum antibiotics for 14 days [11] oral / systemic (beta-lactam, tetracycline, gentamicin, macrolide, quinolone) and / or inhaled (tobramycin, colistin, aztreonam, liposomal ciprofloxacin.). The antibiotic treatment will be an empirical one, covering the main common germs, until a specific pathogen and its sensitivity are detected.

Figure 1. Scheme for long-term treatment with antibiotics (European Respiratory Society Guidelines - 2017)



Pulmonary function control: bronchodilators, long-term oxygen therapy, non-invasive ventilation.

Inflammation control: inhaled corticosteroids, macrolides, and more recently: neutrophil elastase inhibitors5, statins, specific therapy CFTR (cystic fibrosis transmembrane conductance regulator).

Surgical treatment in patients with bronchiectasis. Surgical pulmonary resection may be a treatment option for patients with localized disease, as well as for those with an increased

frequency of exacerbations. Massive hemoptysis requires surgery and / or bronchial artery embolization.

Control of complications and comorbidities: treatment of gastro-oesophageal reflux, ischemic heart disease, etc.

Prophylaxis refers to the proper treatment of pneumonia and pulmonary tuberculosis, immunization against viral infections and pneumococcal pneumonia, routine immunizations from childhood.

The quality of life of patients with bronchiectatic disease remains highly influenced by symptomatic polymorphism and associated comorbidities. Its quantification is done through standardized questionnaires, the most known being St. George QoL Questionnaire.

Bibliography

1. Quint JK, Millett ER, Joshi M et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: A population-based cohort study. Eur Respir J 2016; 47: 186–193.

2. Maselli DJ et al. Suspecting non-cystic fibrosis bronchiectasis: What the busy primary care clinician needs to know. Int J Clin Pract 2017; 71: e12924.

3. Cole PJ. Inflammation: a two-edged sword - the model of bronchiectasis. Eur J Respir Dis Suppl 1986; 147: 6–15.

4. Margarida Redondo et al. Global impact of bronchiectasis and cystic fibrosis. Breathe 2016; 12: 222-235.

5. Chalmers JD, Aliberti S, Blasi F. State of the art: Management of bronchiectasis in adults. Eur Respir J 2015; 45: 1446-62.

6. Corrin B, Nicholson AG. Diseases of the conductive airways, in Pathology of the Lungs - third edition, Curchill-Livingstone Elsevier 2011, pp. 91-134.

7. Aliberti S, Masefield S, Polverino E, et al. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. Eur Respir J 2016; 48: 632–647.

8. Shin Matsuoka et al. Bronchoarterial Ratio and Bronchial Wall Thickness on High-Resolution CT in Asymptomatic Subjects: Correlation with Age and Smoking. American Journal of Roentgenology 2003; 180: 513-518 [10.2214 / ajr.180.2.1800513].

9. Aliberti S, Lonni S, Dore S et al. Clinical phenotypes in adult patients with bronchiectasis. Eur Respir J 2016; 47: 1113–1122

10. McDonnell MJ et al. Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study. Lancet Respir Med 2016 Published Online November 15, 2016 [http://dx.doi.org/10.1016/ S2213-2600 (16) 30320-4].

11. Polverino E, Chalmers JD et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J 2017; 50: 1700629 [https://doi.org/ 10.1183 / 13993003.00629-2017].

12. Mario Silva., Imaging of Bronchiectasis, in Bronchiectasis - The EMBARC Manual, editors: Chalmers J, Polverino E, Aliberti S., Springer International Publishing AG 2018, pp. 9-26 [https://doi.org/10.1007 / 978-3-319-61452-6].

13. Goeminne PC, De Soyza A. Bronchiectasis: how to be an orphan with many parents? Eur Respir J 2016 Jan; 47 (1): 10-3 [doi: 10.1183 / 13993003.01567-2015].

14. Chalmers JD, Goeminne P, Aliberti S et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med 2014; 189: 576-585.

15. McShane PJ et al. Non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2013 Sep 15; 188 (6): 647-56 [doi: 10.1164 / rccm.201303-0411CI].

11. CYSTIC FIBROSIS

1. Definition

Cystic fibrosis (CF) or mucoviscidosis (MV) is the most common potentially lethal monogenic disease of the Caucasian population, with autosomal recessive transmission and manifested by an impressive clinical polymorphism, with respiratory, digestive and even metabolic disorders. Due to the diversity of clinical manifestations and the varying degree of clinical expression, this disease is frequently underdiagnosed.

2.Epidemiology

The incidence of the disease is variable, being from 1: 2000 to 2500 newborns[1] in Europe and the USA. In our country the incidence is 1: 2054, close to the European average. Improvements in the care of CF patients have improved the survival rate up to 40 years.

3. Pathogenesis / Risk factors / Etiology

The genetic substrate of FC consists in the existence of mutations in the gene that regulates the transmembrane conductance of the chlorine-CFTR (cystic fibrosis transmembrane conductance regulator), called the CF gene. In the database of "Cystic Fibrosis Consortium" there are registered over 2000 mutations - over 400 polymorphic variants. The most common mutation is Δ F508, with a European average of 70%. Because many alleles are involved, the genotype of a patient may be homozygous or heterozygote, identified by molecular genetic diagnostic tests. Mutations in the CFTR gene can be classified into six classes depending on the mechanism by which they disrupt the synthesis, circulation, and function of the protein CFTR channel Cl^-.

Increased mucus viscosity, along with oxidative stress, lowering pH associates bronchopulmonary infections with Staphylococcus aureus, Pseudomonas aeruginosa and other pathogens, leading to chronic airway and systemic inflammation. further promoting infections and proinflammatory cytokines that stimulate angiogenesis, inflammation and fibrosis, with tissue destruction and frequent exacerbations leading to loss of lung function and the installation of respiratory failure.

4. Cystic fibrosis clinic

The clinical picture of CF is very varied, the manifestations are with early onset, from the period of infancy, but sometimes the diagnosis is not made during the childhood, especially in patients with atypical forms or with milder clinical expression.

Typical clinical manifestations present in patients with cystic fibrosis are:

- *respiratory signs:* chronic productive cough, with a viscous sputum, in large quantities, mucopurulent, frank purulent - in acute exacerbations, sometimes with faint streaks.
- *digestive signs:* diarrhea steatoreic stools,
- *general signs:* weight deficit in adults and failure of growth in children, stationary / weight loss, despite a good appetite and an adequate nutritional intake.

The clinical picture of the adult with CF may include any of the manifestations:

• chronic cough, tachypnea, wheezing, bronchiectasis, nasal polyposis, recurrent sinusitis, hemoptysis, pneumothorax. Pulmonary hypertension is a possible complication during the course of CF.

• chronic liver disease / cirrhosis, diabetes,

• osteopathy, weight deficit, infertility

Digestive manifestations

Chronic diarrhea, with steatorrhea, is a specific manifestation of CF, due to insufficient exocrine pancreatic secretion, with the reduction or absence of pancreatic enzymes, which generates steatorrhea with reduced fat absorption, but also with severe consequences due to the deficiency of absorption of fat-soluble vitamins (A, D, E, K). Chronic abdominal pain is common in children, but is present also in adults. It may have the following causes: distal intestinal obstruction syndrome (DIOS), gallstones, massive splenomegaly, reflux oesophagitis, occlusive or subocclusive syndromes, fibrotic colonopathy, flatulence, constipation.

Besides respiratory pathology there are manifestations or complications that occur during the course of the disease, of which diabetes in CF (DZCF) and associated hepatopathy CF (HACF) are the most common and most frequent complications.

In the evolution of the disease there may also be osteoarticular manifestations (hypertrophic osteoarthropathy) and mental manifestations / complications: depression, aggression.

5. Microbiology

Respiratory pathology is the determinant element in the evolution of the patient with CF, lung infections being the main cause of morbidity and mortality. Germs commonly founded, considered "traditionals" are *Pseudomonas aeruginosa*, *Staphylococcus aureus, Haemophilus influenza,* and relatively recent germs are *Burkholderia complex, Stenotrophomonas maltophilia,* Achromobacter xylosoxidans, Mycobacteria asuberculica and Canduberculeae, *Aspergillus fumigatus, Candida albicans*.

Pseudomonas aeruginosa infection is a major cause of morbidity and mortality in patients with CF, therefore, early diagnostic and prophylactic treatment of chronic infection depends on the patient's evolution.

First infection with *Pseudomonas aeruginosa* is defined by the first positive culture, when the germ is mobile, low density, nonmucoid strains, did not develop biofilm, at this stage sterilization is possible. Chronic infection with *Pseudomonas aeruginosa* is accompanied by an increased frequency of exacerbations, loss of lung function and shortened lifespan. Pseudomonas infection is defined as: intermittent: when cultures are positive in <50% of annual crops (at least 4 samples / year), chronic: positive in> 50% of annual cultures.

Staphylococcus aureus is the most common germ isolated in children with CF in the first decade of life, may be associated with Haemophilus influenza, Pseudomonas aeruginosa, Bulkholderia cepacia or other gram-negative germs.

Methicillin-resistant Staphylococcus aureus (MRSA) is a reducible germ, with increasing prevalence, the source of infection being nosocomial but also community, and the infection occurs mainly in patients with poor lung function. MRSA infection can be chronic, with an evolutionary pattern similar to Pseudomonas infection, but with slower progressive evolution in most patients.

Burkholderia complex. B. Cenocephacia infection causes rapid clinical deterioration and death in more than one third of patients, but there are also patients with good progress despite chronic Burkholderia infection.
Allergic bronchopulmonary aspergillosis is considered as a complication of respiratory distress, representing an allergic response of bronchial epithelium to Aspergillus fumigatus infection (12% of CF patients). Clinically manifested with wheezing, fever, the appearance of specific pulmonary changes.

6. Paraclinical investigations

- Represented by: complete CBC, ionogram, liver tests (ALT, AST, Gamma GT), Dose of fat-soluble vitamins: D, A, E, markers of inflammation (VSH, CRP, procalcitonin), dosage of serum amylases and lipases, total IgE, Aspergillus specific IgE
- Microbiology. It is recommended to carry out bacteriological investigations on a monthly basis, or at any sign of exacerbation or infection. In infants can be harvested: pharyngeal exudate, hypopharyngeal aspirate, and in the largest sputoculture or culture from the secretions obtained by induced sputum.
- Fecal elastase is low in CF, in those with pancreatic insufficiency (usually <15 μ / g in CF patients).

Imaging investigations in CF
A simple chest X-ray may reveal diffuse peribronchial thickening, emphysema, segmental and subsegmental atelectasis, confluent reticulo-nodular opacities, bronchiectasis. Computed tomography (CT) is a more sensitive method of detecting early changes in FC. It is recommended to be done with high resolution, at 2 years or in cases where a complication is suspected. The changes specifically described in patients with CF are variable, depending on the evolution, from the incipient bronchiectasis, tubular, tree-in-bud, even the sacciform, full of secretions or abscesses, emphysema (air trapping), blockages by mucus plugs (mucus plugging), atelectasis, fibrosis secondary to infections, rarely condensation or pleural involvement.
Functional lung tests

- Spirometry - reveals an obstruction syndrome, initially only distal, expressed by decreasing MEF25 or FEF 25-75; the parameters used as evaluation of the obstruction are FEV1, FEF25-75%, IPB, which fall below 80%
- Pulmonary clearance index (PCI) is the most specific parameter that evaluates lung function; is a non-invasive test that requires passive cooperation and can be performed in children <5 years old; it reveals early changes of pulmonary heterogeneity.

Abdominal ultrasound is recommended as an annual ultrasound screening for the detection of hepatopathy in children with CF, or biannually in those with associated hepatopathy.
Bone mineral density assessment (DEXA) is recommended for patients > 10 years as screening for those with secondary CF osteopathy and those receiving long-term oral steroids or who have had prolonged / multiple treatments in the previous year.
Bronchoscopy is indicated for the collection of broncho-alveolar lavage in patients with persistently altered clinical condition in whom the pharyngeal cultures / induced sputum are negative, or for therapeutic purposes those with mucus plug atelectasis (instillations with alpha dornase rhDNase = 2.5 mg diluted with 10 ml saline)

7. Positive diagnosis

Early diagnosis and prompt and correct treatment of the disease reduce morbidity and mortality through complications, ensure optimal quality of life of the patient for a long time and social insertion of the adult with CF.
Classically, the diagnosis of CF starts from the characteristic clinical-anamnestic elements and is confirmed by the sweat test, considered "gold standard" of diagnosis. The method involves the initial stimulation of transpiration with pilocarpine, followed by measuring the amount of chlorine from the sweat collected through a collector, using a macroduct apparatus (Normal <30 mMol (mEq) / l, Equivocal between 30-60 mMol (mEq) / l - must be repeated and interpreted in clinical context, positive> 60 mMol (mEq) / l
There are atypical, rare forms of cystic fibrosis, where the test is negative; these forms have "milder" mutations, and the genetic test is diagnostic.

Genetic diagnosis

The genotype is determined by molecular genetic test, which can show a homozygous genotype (the same mutation inherited from both parents), or heterozygous (one mutation from the mother and another from the father). The identification of both pathological alleles represents the absolute confirmation of the diagnosis and the genetic test must be performed in all patients with suspected CF.
In order to objectify the pancreatic insufficiency, it is recommended to measure in the stool the pancreatic fecal elastase PFE 1, its low values are the proof of the pancreatic insufficiency.

8. Differential diagnosis of CF is very difficult and is made depending on the respiratory or digestive manifestations. Among the respiratory diseases are: alpha1-antitrypsin deficiency, bronchiectasis of various etiology (syndromatic, immunodeficiency, infectious), tuberculosis, severe asthma, and digestive diseases - exocrine pancreatic insufficiency, celiac disease, cirrhosis, secondary diabetes, etc.

9. Treatment

Cystic fibrosis pneumopathy therapy

The pulmonary pathology present in the patients with CF involves a multidisciplinary approach, having as objectives: the control of the pulmonary infections, the reduction of the inflammation, the improvement of the mucociliary clearance, in order to preserve the lung function, to prevent the complications and to obtain an optimal nutritional status for a satisfactory quality of life.
Treatment includes mucolytic medication, respiratory physiotherapy and the treatment of respiratory infections. To these is added a prophylactic component of prevention of infections through rigorous hygiene and specific vaccination (influenza, anti-pneumococcal etc).

Physiotherapy

The daily physiotherapy of the patient with CF includes: respiratory clearance techniques, physical exercises and individually tailored methods to help eliminate secretions. The physiotherapy techniques will be chosen according to the patient's age, clinical-evolutionary status, preferences and compliance, with the help of the specialized physiotherapist on respiratory physiotherapy and cystic fibrosis.

Mucolytic therapy

-favors the elimination of the viscous mucus, preventing stagnation and secondary over-infections. Mucolytics are given by inhalation, the most effective and recommended are hypertonic saline solutions, deoxyribonuclease (rh-DNA-za), N-acetylcysteine, aerosol therapy.

Antibiotics

The main goals of antibiotic therapy in CF are the prevention, eradication and control of respiratory infections associated with FC.
General principles of antibiotic therapy: aggressive treatment from the beginning, in doses higher than in other conditions, guided treatment depending on the severity of the symptoms and the isolated germ, prolonged treatments of 3-4 weeks; obligatory in the moments of exacerbation begins with intravenous treatment associated with inhaled antibiotics.

Treatment of *Pseudomonas aeruginosa* infection
First infection - the first positive culture

- First intention: Ceftazidim iv + Amikacin - 14 days
- Ciprofloxacin oral 14-21 days, when the general condition is good

In chronic infection with Pseudomonas it is recommended:
-Tobramycin inhaler, 2x1 vial / day, 28 days, then 28 days pause, repeat treatment, for 6 months or inhaled colimicin, 2x1 cps or vial / day, daily
- Chronic therapy with Azithromycin, 10 mg / kg body / day, single dose, 3 days / week, at 2 weeks or weekly, 6 months, if lung function is reduced. For the protection against ototoxicity it is recommended the association of oral N-acetylcysteine, during the therapy with aminoglycoside iv.
Regular intravenous antibiotic treatment at 3 months may be recommended in cases of moderate / severe respiratory dysfunction and chronic respiratory failure.
Treatment of Staphylococcus aureus infection
First infection with good clinical status: oral antibiotic: Amoxicillin + clavulanic acid or Azithromycin / Clarithromycin or quinolone - 1 month. If the clinical condition is altered: last generation cephalosporin + Amikacin (or Tobramycin). In chronic infection- Amoxicillin + clavulanic acid 100 mg / kg body / day or Rifampicin.
Treatment of methicillin-resistant Staphylococcus aureus (MRSA) infection
In the case of a first infection, with good clinical condition, eradication with oral antibiotic therapy: Cotrimoxazole associated with Rifampicin, for 1 month. If the clinical condition is altered: antibiotic iv: Vancomycin or Teicoplanin or Linezolid (with monitoring of probable hematological side effects)
Treatment of infection with non-tuberculous mycobacteria (MNTB)
MNTB includes several species, of which M. abscessus complex has significant pulmonary effects. M. abscessus infection benefits from iv antibiotic therapy with imipenem, amikacin, quinolones, 3 weeks later, 18-24 months oral consolidation therapy: rifampicin, azithromycin, ethambutol +/- inhalation. Sterilization is defined by 4 negative cultures during one year, after the end of the treatment, the failure of eradication implies the chronic administration of antibiotic in double association.
Treatment of Aspergillus fumigatus (ABPA) infection
Prednisone 0.5-1 mg / kg body / day at least 14 days. Oral corticosteroids are associated with antifungals.
Treatment of viral infections
- predispose to bacterial over infection, often the first isolation of Ps. aeruginosa occurs after a viral infection, therefore, even if they are of viral etiology, prophylactic antibiotic treatment is recommended.
Treatment of pulmonary complications such as atelectasis, pneumothorax, hemoptysis, etc. it is done only by hospitalization in specialized clinics.

NSAIDs

Nonsteroidal anti-inflammatory drugs - can be given to patients over 6 years of age with mild ventilatory dysfunction.

Corticotherapy - Oral CS is recommended only in bronchopulmonary aspergillosis, Inhalatory CS is not effective in patients with cystic fibrosis. They can be used as a background therapy, in cases where an asthma is diagnosed (bronchial hyperreactivity).

Bronchodilators

Beta 2-short-term inhalers are only recommended for patients who associate bronchial hyperreactivity or before the inhaled treatement medication (antibiotics, mucolytics), or if they cause coughing, dispnea or wheezing; in those with allergic bronchopulmonary aspergillosis (ABPA), asthma associated with mucoviscidosis, asthma-like symptoms

Lung transplant

Since 1985, lung transplant has become an option for some patients with MV. Most centers today prefer sequential bilateral transplantation which has the advantage of keeping its own heart.

Management of pancreatic insufficiency

Pancreatic enzyme replacement therapy (TSEP) of pancreatic insufficiency is performed with Kreon minimicrospheres, according to age, without exceeding 10,000 IU lipase / kg body / day. The correct dose will be adapted to each patient and nutritional input and it is that dose that corrects steatorrhea, abdominal pain and decreases the frequency and number of stools.

Treatment of hepatopathy associated with FC

After establishing the diagnosis, ursodeoxicolic acid will be introduced in the dose of 15-20 mg / kg body / day, in two doses, permanently. The treatment of complications is recommended to be done in the compartments of gastroenterology and hepatology.

Treatment of nutrition disorders

Good nutritional status represents a significant predictive factor of the survival of patients with CF. There is a close correlation between body weight and lung function; almost all terminally ill patients have severe malnutrition. Nutritional interventions consist of behavioral treatment, psychological support, dietary advice, oral supplementation, well feeding, gastrostomy, parenteral nutrition.

10. Evolution and prognosis

The evolution is dictated by the lung status, and the prognosis conditioned by the presence of associated lung infections but also by the presence of complications. Life expectancy of patients with cystic fibrosis varies around the age of 35-40 years.

The evolution is marked by exacerbations of pulmonary infections. Pulmonary exacerbation can be manifested by: increasing sputum production and / or changing its appearance, de novo hemoptysis or exacerbation of pre-existing microhemoptysis, coughing, dyspnea, asthenia, fatigue, lethargy, weight loss, anorexia, decreased FEV 1 or FVC more than 10% compared to the basic value of the last 3 months; fever> 38 ° C, new radiological changes, specific, new rales.

11. Preventive measures

The prophylaxis of the disease can be done only through the genetic advice addressed to the carriers of a mutation producing CF. Regarding the prophylaxis of infections in the FC, there are currently some standards that are required. For the prophylaxis of infections it is recommended to segregate patients, in order to prevent cross infections.

Bibliography

1. Rowe S., Miller B.S., J. Sorscher, .- Cystic Fibrosis-N Engl.Med J 2005 352: 1992–2001
2. Knowles MR, Durie PR. What is cystic fibrosis? N Engl J Med 2002; 347: 439-442
3. Popa I., Nicolau S., Cristescu A., Zagorca Popa et al: Results of a pilot study in the detection of newborns with mucoviscidosis, Pediatrics, 1988, 2, 151-158
4. Bush A et al (Eds). Cystic Fibrosis in the 21st Century. Progress in Respiratory Research. Basel, Karger. 2006; 34: 251-61
5. Dodge, J.A., Lewis, P.A., Stanton, M., and Wilsher, J. Cystic fibrosis mortality and survival in the UK: 1947–2003.European Respiratory Journal, 2007; 29: 522-526
6. Smyth A., Bell S.C., Bojcind S., Bryon M., Duff R., Flume P.A. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines - Journal of Cystic Fibrosis 13 (2014) S23 – S42
7. Popa I., Pop L. Mucoviscidoza, map
8. Popa I., Pop LL, Popa Z., Calt C., - Management guide in mucoviscidosis (cystic fibrosis) - Magazine
9 Doring G., Conway S., Hoiby N., Antibiotic therapy against Pseudomonas aeruginosa in CF: EurRespir J 2000;
10. Flume, P.A., Mogayzel, P.J., Robinson, K.A., Goss, C.H., Rosenblatt, R.L., Kuhn, R.J. et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care Med. 2009; 180: 802–808
11. Kerem E., et al. Standards of care for patients with cystic fibrosis: Journal of Cystic Fibrosis 2005
12. Langton-Hewer, S.C. and Smyth, A.R. Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. Cochrane Database Syst Rev. 2006;.(updated 2010)
13.Antibiotic treatment for cystic fibrosis. Report of the UK Cystic Fibrosis Trust Antibiotic Group. UK Cystic Fibrosis Trust, London; 2009
14. Mogayzel, P.J., Naureckas, E.T., Robinson, K.A., Mueller, G., Hadjiliadis, D., Hoag, J.B. et al. Cystic fibrosis pulmonary guidelines. Am J RespirCrit Care Med. 2013; 187: 680–689
15. Pressler T. , Bohmova C., Conway S., Dumcius S., Hjelte L., Hřiby N., Kollberg H., Tümmler B., Vavrova V., Chronic Pseudomonas aeruginosa infection definition: EuroCareCF
Working Group report Journal of Cystic Fibrosis Volume 10 Suppl 2 (2011) S75–S78
16. Schuster, A., Haliburn, C., Döring, G., and Goldman, M.H. Group ftFS. Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study. Thorax. 2013; 68: 344–350
17. Oermann, C.M., Retsch-Bogart, G.Z., Quittner, A.L., Gibson, R.L., McCoy, K.S., Montgomery, A.B. et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol. 2010; 45: 1121–1134
18. Southern, K.W., Barker, P.M., Solis-Moya, A., and Patel, L. Macrolide antibiotics for cystic fibrosis. Cochrane Database Syst Rev. 2012;
19. Flume P.A., O'Sullivan K.P., Robinson KA, Goss C.H., et al - Cystic Fibrosis Pulmonary Guidelines-Chronic Medications for Maintenance of Lung Health American Journal Of Respiratory and Critical Care vol 127, 2007
20. Smyth AR., Prophylactic anti-staphylococcal antibiotics for cystic fibrosis. Cochrane Database Syst Rev. 2012 Dec
21. Vandamme P et al Burkholderia cenocepacia sp. nov.—a new twist to an old story. Res Microbiol 2003
22. Ciuca I.M, Pop L.L, Urgente in mucoviscidoza, capitol in Urgente in bolile rare , 2014

12. PLEURAL EFFUSIONS

Definition

Pleural effusion is an abnormal collection of fluid in the pleural space, usually resulting from excess fluid production and / or decreased lymphatic resorption. It is the most common manifestation of pleural pathology, whose extremely broad etiological spectrum includes cardiovascular diseases, systemic inflammatory diseases, infectious diseases, endocrinological diseases, malignancies etc.

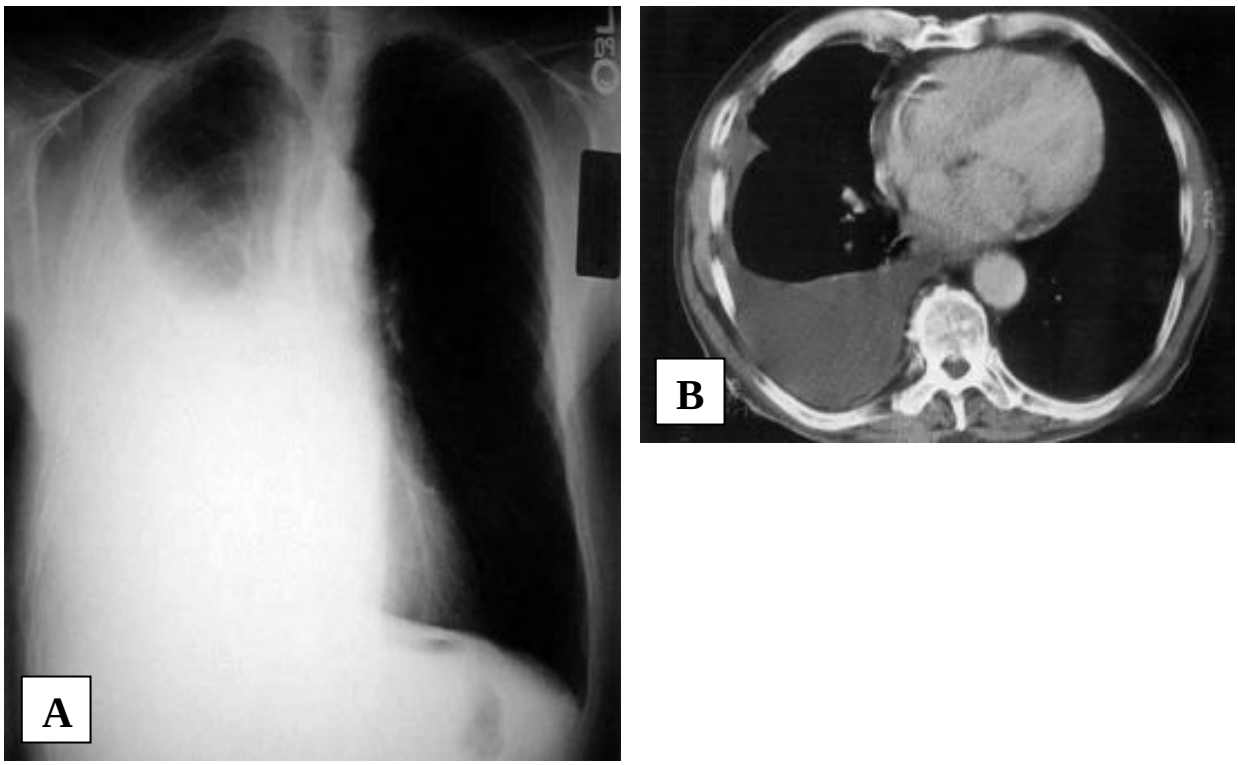


Fig. 1 A. Right pleural effusion of malignant etiology.
B. Medium sized right pleural effusion evidenced by the CT scan of the thorax

Epidemiology

The exact incidence of pleural effusions is difficult to determine because they are usually the manifestation of an underlying pathological process. Worldwide, the prevalence of pleural effusions is estimated at 320 cases per 100.000 inhabitants in industrialized countries, with a distribution of etiology reflecting the prevalence of underlying conditions. In the United States, an incidence of at least 1.5 million new cases is estimated annually.

Anatomy and physiology of the pleura

The pleural cavity is the virtual space between the parietal and the visceral membranes of the pleura. The parietal pleura covers the thoracic wall and the surface of the ribs, from which it is separated by a layer of connective tissue, and at the level of the hila, it forms a sleeve that

surrounds the large vessels and the main bronchi. The pleura is irrigated by vessels from systemic circulation and is richly innervated. Visceral pleura wraps the lungs, penetrating into the interlobular fissures, and has no innervation. The right and left pleural cavities are separated in healthy subjects by the anterior and posterior mediastinum.

The pleura has a membranous structure, with the surface covered by a layer of mesothelial cells with microvilli where the processes of formation and absorption of the pleural fluid take place. The latter has the role of lubricating the pleural sheets, reducing the frictional forces between the lung and thoracic wall. The fluid is permanently formed at the level of the parietal pleural surface by a plasma ultrafiltration process (approx. 1 liter / day) and is resorbed either in the capillaries of the visceral pleura, or through the lymphatic system of the parietal pleura, so that the amount of fluid in the pleural space does not normally exceed 20-30 ml. Under pathological conditions, the fluid from the pleural space may also come from the pulmonary interstitial space through the visceral pleura or from the peritoneal cavity through the pores of the diaphragm.

Etiology

The small amount of pleural fluid normally present in the pleural space is maintained at a constant level by the fine balance between the hydrostatic and oncotic pressures and by continuous drainage through the peripheral lymphatic vessels. The alteration of this balance is at the origin of fluid accumulation in the pleural space.

The presence of a pleural effusion signals the existence of an underlying pathological process of pulmonary or extrapulmonary origin, which in turn may have an acute or chronic evolution. Although the etiologic spectrum is extremely wide, most pleural effusions are caused by congestive heart failure, pneumonia, malignancy or pulmonary embolism.

The mechanisms that may play a role in the accumulation of fluid in the pleural cavity are summarized below:

- Permeability alteration of the pleural membranes (e.g. inflammation, tumor invasion, pulmonary embolism)
- Decreased intravascular oncotic pressure (e.g. hypoalbuminemia in nephrotic syndrome or liver cirrhosis)
- Increased capillary permeability or vascular destruction (e.g. trauma, neoplasia, inflammation, pulmonary infarction, drug-induced hypersensitivity reaction, uremia, pancreatitis)
- Increased capillary hydrostatic pressure in the systemic and / or pulmonary circulation (e.g. congestive heart failure, superior vena cava syndrome)
- Decreased pressure in the pleural space due to inability of the lung to fully expand during inspiration; this situation is called "trapped lung" and may be due to an obstructed bronchus or contraction from fibrosis leading to restrictive syndrome
- Decrease or complete blockage of the lymphatic drainage, including obstruction or rupture of the thoracic duct (e.g. malignancy, trauma)
- Abnormal passage of the peritoneal fluid into the pleural cavity across the diaphragm by microperforated extravasation via lymphatics, or microstructural defects of the diaphragm (e.g. hepatic hydrothorax, cirrhosis, peritoneal dialysis)
- Movement of fluid from pulmonary edema across the visceral pleura
- Persistence of increased oncotic pressure in the pleural fluid in case of an existing pleural effusion, which can lead to further accumulation of fluid.

Pleural effusions are generally classified as transudates or exudates, depending on the generative mechanism and the biochemistry of the pleural fluid. The transudates result from alteration of the balance of oncotic and hydrostatic pressures, while the exudates are due to inflammatory pleural processes and / or low lymphatic drainage. In some situations, the pleural effusion may have mixed characteristics of transudate and exudate.

Transudates

Transudates have a limited, well-defined number of causes including:

- Congestive heart failure
- Liver cirrhosis (hepatic hydrothorax)
- Atelectasis (may be due to occult malignancy or pulmonary embolism)
- Hypoalbuminemia
- Nephrotic syndrome
- Peritoneal dialysis
- Myxoedema
- Constrictive pericarditis
- Extravascular migration of a central venous catheter

Exudates

They are caused by a variety of diseases that lead to inflammation of the pleural membranes (often requiring a more extensive evaluation and treatment strategy than in the case of transudates) or by decreased lymphatic drainage of the pleura.

The most common causes of exudative pleural effusion include:

- Pneumonias (parapneumonic pleural effusion)
- Neoplasms (most common: lung or breast cancer, lymphomas, leukemias; less common: ovarian carcinoma, gastric cancer, sarcomas, melanomas)
- Pulmonary embolism
- Collagenosis (rheumatoid arthritis, systemic lupus erythematosus)
- Tuberculosis
- Pancreatitis
- Chest injuries
- Post-cardiac injury syndrome
- Esophageal perforation
- Radiation pleuritis
- Sarcoidosis
- Fungal infections
- Pancreatic pseudocyst
- Intra-abdominal abscess
- Status post coronary artery bypass graft (CABG) surgery
- Pericardial disease
- Meigs syndrome (benign pelvic tumor with associated ascites and pleural effusion)
- Ovarian hyperstimulation syndrome
- Drug - induced pleural disease (check the Pneumotox.com website for an extensive list of medications that may cause pleural effusion)
- Pleural asbestosis
- Yellow nail syndrome (yellow nails, lymphedema, pleural effusions)

- Uremia
- Trapped lung (localized healing of the pleura with the formation of fibrous tissue that prevents the full expansion of the lung, sometimes causing pleural effusion)
- Chylothorax (acute condition with increased triglycerides in the pleural fluid)
- Pseudochylotorax (chronic condition with elevated cholesterol in the pleural fluid)
- Fistula (ventriculo-pleural, bilio-pleural, gastro-pleural)

History

A complete and carefully conducted anamnesis is absolutely necessary for the assessment of pleural effusions, providing important clues for establishing the etiology. For example, a history of chronic hepatitis or alcoholism and the presence of clinical signs of cirrhosis may suggest liver hydrothorax or alcohol-induced pancreatitis with secondary pleural effusion. A history of recent trauma or surgery on the thoracic spine may raise the suspicion of cerebrospinal fluid leakage. A history of malignancy, even in the more distant past, is also important, because malignant pleural effusion can develop years after the initial diagnosis.

Patients should also be questioned about their occupational exposure to various harmful substances, including asbestos, which predisposes to secondary pleural effusion of a malignant mesothelioma or a benign asbestos related pleural disorder. It is also important to note the concomitant medication the patient is administering.

Clinical manifestations of pleural effusion are variable and usually reflect the underlying pathological process. The most commonly associated symptoms are: progressive dyspnea, cough and pleuritic chest pain.

Dyspnea

Dyspnea is the most common symptom associated with pleural effusion and is due to distortion of the diaphragm and chest wall during breathing rather than hypoxemia. This is supported by the fact that in many patients the drainage of the pleural fluid improves the dyspnea even with limited improvement in gas exchange. Pleural fluid drainage also allows easier recognition of the underlying disease on the control chest X-ray. It is worth noting that, sometimes, dyspnea can be caused by the disease that led to the formation of pleural collection, such as underlying intrinsic lung or cardiac disease or endobronchial obstructive lesions, rather than by the effusion itself.

Cough

It is usually mild and nonproductive. A more severe cough or the presence of purulent and / or bloody sputum usually suggests pneumonia or endobronchial injury.

Chest pain

It is given by the irritation of the pleural membranes, and its presence suggests the probability of an exudative etiology, such as pleural infection, mesothelioma or pulmonary infarction.

Physical examination

The changes that can be noted at the physical examination depend on the size of the pleural effusion. For small pleural collections (< 300 mL), physical examination may be normal.

In the case of pleural effusions > 300 mL, the following diagnostic changes can be detected

- Asymmetrical respiratory movements, with diminished or delayed thoracic excursions on the side of the pleural collection
- Decreased tactile fremitus

- Dullness to percussion
- Decreased or abolished breath sounds
- Egophony (at the upper edge of the pleural collection)
- Pleural friction rub

Mediastinal shift away from the pleural collection side can be observed in case of pleural effusions of > 1000 mL. If the trachea and mediastinum are moved toward the side of the pleural collection, this may be a sign of a lobar bronchus obstruction by an endobronchial lesion of malignant or non-malignant etiology (foreign body).

Sometimes the objective examination may reveal signs of the underlying disease that led to the formation of pleural effusion:

- Peripheral edema, distension of jugular veins, abnormal heart sounds (S3 gallop) may indicate the presence of a heart failure
- Edema may also be a manifestation of a nephrotic syndrome, pericardial disease or, if associated with yellow nail bed coloration - yellow nail syndrome
- The presence of cutaneous lesions and ascites are suggestive for liver cirrhosis
- Limphadenopathy or a palpable mass may suggest malignancy

Diagnostic workup

Thoracentesis should always be performed in the case of a new pleural effusion with no obvious cause, if there is a sufficient amount of fluid to allow the procedure to be performed safely. The simple observation is acceptable if a benign etiology is likely, such as in the context of heart failure, viral pleuritis, or a recent history of thoracic or abdominal surgery.

Discrimination between a transudative versus an exudative pleural effusion is usually done by means of laboratory tests. However, sometimes the macroscopic aspect of the fluid obtained during thoracentesis can raise the suspicion of certain types of exudates:

- Frankly purulent fluid indicates an empyema
- A putrid odor suggests an anaerobic empyema
- A milky white, opalescent appearance of the pleural fluid suggests a chylothorax, most often resulting from lymphatic obstruction by malignancy or thoracic duct injury by trauma or surgical procedure
- Haemorrhagic pleural fluid may result from trauma, malignancy, postpericardiotomy syndrome or asbestos related pleural damage. A pleural fluid hematocrit level of > 50% of the peripheral hematocrit level defines a hemothorax, which often requires tube thoracostomy
- Black pleural fluid suggests a limited number of possible etiologies, including infection with Aspergillus niger or Rizopus oryzae, malignant melanoma, non-small cell lung cancer, rupture of a pancreatic pseudocyst or charcoal containing empyem.

Normal pleural fluid has the following characteristics:

- clear ultrafiltrate of plasma originating from parietal pleura
- pH = 7.60 - 7.64
- protein content < 2% (1-2 g / dL)
- cellularity < 1000 leukocytes / mm
- glucose content similar to that of plasma
- LDH <50% of plasma LDH

The first step in establishing the etiology of a pleural effusion is to classify it as a transudate or exudate. Over time, several biochemical tests have been proposed for the differentiation between exudates and transudates; however, the tests initially proposed by Light and collaborators have become standard criteria.

The pleural fluid is considered an exudate if at least one of the following criteria is met, and in their absence, is a transudate:

1. Pleural protein / serum protein > 0.5
2. Pleural LDH / serum LDH > 0.6
3. Pleural LDH > 2/3 of the normal upper limit of serum LDH level

Pleural fluid biochemistry

Levels of pleural LDH > 1000 IU / L suggest empyema, malignant pleural effusion, rheumatoid effusion or pleural paragonimiasis. Pleural LDH also increases in pleural effusions associated with Pneumocystis jiroveci (previously, P. carinii) pneumonia. In these cases, the diagnosis is suggested by a ratio of pleural LDH / serum LDH > 1, with a ratio of pleural protein / serum protein < 0.5.

Additionally, routine glucose and pH measurement during the initial thoracentesis is recommended. A low concentration of pleural glucose (30-50 mg / dL) suggests malignancy, TB pleuritis, esophageal rupture or lupus pleuritis. Very low concentration of pleural glucose (< 30 mg / dL) further narrows the spectrum of possible etiologies to rheumatoid pleuritis or empyema.

The pH level of the pleural fluid has a good correlation with the level of pleural glucose. A pleural pH < 7.30 in the context of a normal arterial pH is caused by the same conditions listed above for the situation when the pleural glucose is low.

Pleural fluid cell count differential

If an exudate is clinically suspected or confirmed by biochemical tests, pleural fluid samples should be sent to the laboratory for total and differential cellularity measurement, for microbiological and cytological examination.

Pleural fluid lymphocytosis, with lymphocytes > 85% of all nucleated cells, suggests TB, lymphoma, sarcoidosis, chronic rheumatoid pleuritis, yellow nail syndrome or chylothorax. Values of pleural lymphocytes of 50-70% of the nucleated cells suggest a malignant disease.

Pleural fluid eosinophilia (PFE), with eosinophil values > 10% of nucleated cells, is found in about 10% of pleural effusions and does not correlate with peripheral blood eosinophilia. PFE is most often caused by the presence of air or blood in the pleural space. Blood in the pleural space that generates PFE may be the result of pulmonary embolism with infarction or benign asbestos related pleural effusion. Pleural eosinophilia may also be associated with non-malignant conditions, including parasitic diseases (especially paragonymiasis), fungal infections (coccidioidomycosis, cryptococcosis, histoplasmosis) and various medications.

Mesothelial cells can be found in variable proportions in most pleural effusions, but their presence at values > 5% of the total nucleated cells makes the diagnosis of TB less likely. High values of mesothelial cells, especially in bloody or eosinophilic effusions, suggest pulmonary embolism as a probable cause of the pleural effusion.

Pleural fluid culture and cytology

Cultures of infected pleural fluids on the usual media yield a positive result in about 60% of cases. The diagnostic yield is even lower when it comes to anaerobic germs, but can be improved by culturing the pleural fluid directly into the blood culture bottles.

The suspicion of malignant pleural effusion is elevated in patients with a history of cancer or in the presence of an exudate with predominance of lymphocytes, especially if the macroscopic aspect is hematic. The tumor invasion of the pleura can be simply demonstrated by performing the cytological examination of the pleural fluid.

Tuberculous pleuritis

It is usually suspected in patients with a history of TB contact or positive PPD test and an exudative effusion with predominance of lymphocytes, especially if mesothelial cells are less than 5%.

Because most tuberculous pleural effusions result from a hypersensitivity reaction to Mycobacterium rather than microbial invasion of the pleura, direct microscopic examination of a fluid sample (Ziehl-Neelsen) is rarely diagnostic (< 10% of cases), and culture on specific media is positive in less than 65% of cases. In contrast, the concomitant use of histopathological examination and culture of pleural tissue obtained by biopsy increases the diagnostic yield for TB to 90%.

Increased values of adenosine deaminase (ADA) in the pleural fluid > 43 U / mL support the diagnosis of TB pleuritis, but this test has a sensitivity of only 78%. Thus, pleural ADA values < 43-50 U / mL do not exclude the diagnosis of TB pleuritis.

Additional laboratory tests

Additional specific tests are justified when certain etiologies are suspected. For example, assessing the level of amylase in the pleural fluid is required in case of suspicion of pancreatic origin or esophageal rupture or in the situation where a left unilateral pleural effusion remains undiagnosed after the usual tests. It should be noted that amylase in the pleural fluid may also be increased in the context of a malignancy. An additional analysis of amylase isozymes may distinguish between a pancreatic origin of the effusion (diagnosed by the presence of increased pancreatic isozymes in the pleural fluid) and other etiologies.

The level of triglycerides and cholesterol should be measured in the pleural fluid when its milky, white macroscopic appearance raises the suspicion of chylothorax or pseudochilothorax.

Immunological tests, including antinuclear antibodies and rheumatoid factor in the pleural fluid, should be considered when collagenosis is suspected.

Chest radiography

Pleural collections greater than 175 mL can be evidenced on standard chest radiography (postero-anterior incidence, orthostatic position) as blunting of the costophrenic angle. On the chest X-rays performed in supine position, as is often the case in intensive care units, pleural effusions in moderate to large quantities appear as a homogeneous opacification of the lower pulmonary fields. Apparent elevation of the hemidiaphragm, lateral displacement of the diaphragmatic dome or an increase in the distance between the left hemidiaphragm and the gas bubble of the stomach may suggest the presence of infrapulmonary collections.

Computed tomography and ultrasonography

Ultrasonography at the patient's bed has become the standard of care in many hospitals. Contrast enhanced computed tomography should be performed on all patients with an undiagnosed pleural effusion, with the aim of showing thickening of the pleura or signs of invasion of the neighboring structures.

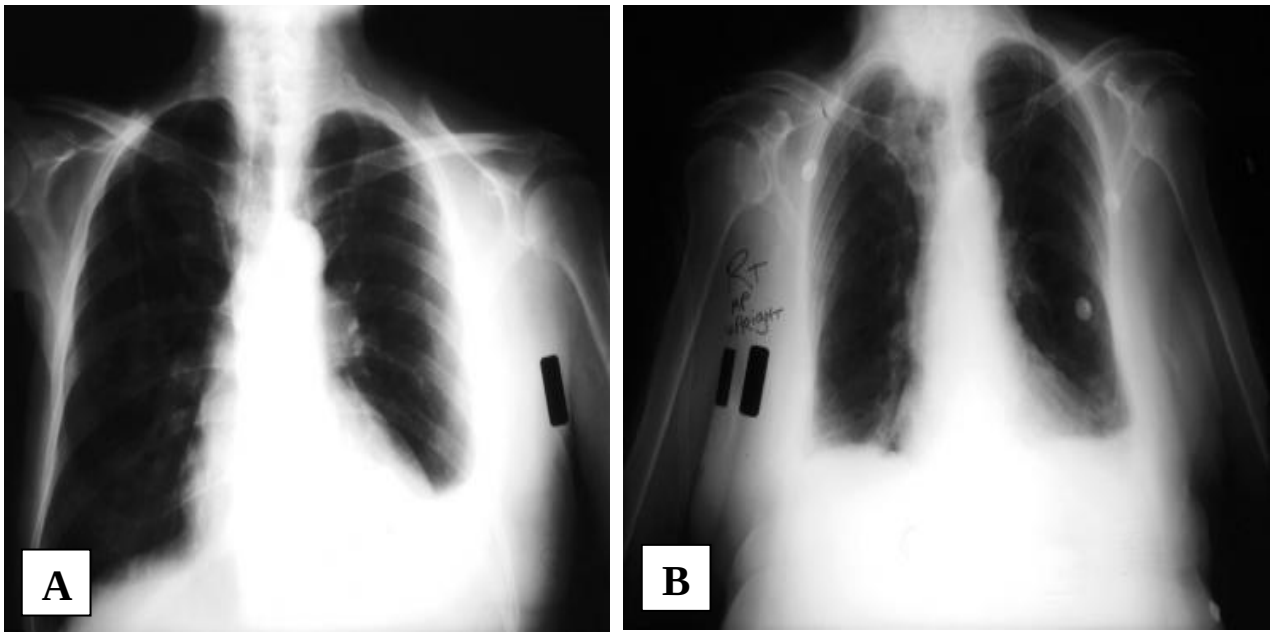


Fig. 2. A. Isolated left pleural effusion, with no visualization of the left costophrenic angle. B. Bilateral pleural effusion with absence of visualization of bilateral costophrenic angles (meniscus sign)

Diagnostic thoracentesis

Thoracentesis for diagnostic purposes should be performed when the etiology of the pleural effusion is uncertain or when the etiological treatment of the alleged cause is not effective. Small pleural collections that present a risk at punctuation or pleural effusion in clinically stable patients with a history of congestive heart failure or a recent thoracic or abdominal surgery, do not require thoracentesis.

Relative contraindications of diagnostic thoracentesis include: small volume of fluid (< 1 cm thickness on lateral decubitus chest X-ray), hemorrhagic diathesis or systemic anticoagulation, mechanical ventilation or skin lesions in the area proposed for puncture. An uncooperative patient is an absolute contraindication for this procedure.

Complications of thoracentesis include pain at the site of puncture, cutaneous or internal bleeding due to injury of an intercostal artery or puncture of the spleen / liver, pneumothorax, empyema, pulmonary re-expansion edema, malignant seeding of the thoracentesis tract or adverse events related to the anesthetics used in the procedure.

Diagnostic pleural puncture can be usually performed safely in patients who have a free collection in the large pleural cavity and who have no relative contraindications to this procedure. The puncture site is chosen according to the radiographic image, and located 1-2 intercostal spaces inferior to the upper limit of the dullness as determined by percussion. In certain situations, ultrasound or tomographic guidance is required.

Pleural biopsy

It should be considered only when there is a suspicion of tuberculosis or malignancy. Medical thoracoscopy performed on the patient in conscious sedation and under local anesthesia was established as a diagnostic method by which a bioptic specimen from the parietal pleura can be taken under direct visual control in cases of undiagnosed exudative pleural effusion. Alternatively, pleural biopsy with a closed needle is a blind maneuver, which can be performed at the patient's bedside.

Differential diagnosis

The following entities should be considered in the differential diagnosis of transudative pleural effusions:

- Congestive heart failure (most common)
- Liver cirrhosis
- Nephrotic syndrome
- Peritoneal dialysis
- Hypoproteinemia
- Glomerulonephritis
- Superior vena cava syndrome
- Cardiac surgery (Fontan procedure)
- Urinothorax
- CSF leak in the pleural space

The differential diagnosis of exudative pleural effusions should include:

- Malignancy
- Pneumonia
- Tuberculosis
- Pulmonary embolism
- Fungal infections
- Pancreatic pseudocyst
- Intra-abdominal abscess
- Post CABG surgery
- Post cardiac injury syndrome
- Pericardial disease
- Meigs syndrome
- Ovarian hyperstimulation syndrome
- Rheumatoid pleuritis
- Systemic lupus erythematosus
- Drug-induced pleural disease
- Asbestos related pleural effusion
- Yellow nail syndrome
- Uremia
- Trapped lung
- Chylothorax
- Pseudochylothorax
- Acute respiratory distress syndrome
- Chronic pleural thickening

- Malignant mesothelioma
- Hypothyroidism

Other possible causes of pleural effusion or which may mimic pleural effusion are as follows:

- Congestive heart failure and pulmonary edema
- Diaphragmatic injuries
- Rupture of the esophagus
- Hypothyroidism and myxedema coma
- Lung neoplasm
- Pancreatitis
- Q fever
- Rheumatoid arthritis

Treatment

The treatment of transudative pleural effusions is always addressed to the primary cause. Drainage should be performed in case of large, refractory pleural effusions causing significant respiratory symptoms.

The management of exudative pleural effusion depends on the underlying etiology of the effusion. Pneumonia, neoplasms and tuberculosis are the most common causes of exudative pleural effusion, the rest being classified as idiopathic.

Complicated pleural effusions and empyema should be drained to prevent fibrosing pleuritis. In patients with malignant pleural effusions, the drainage is done for palliative purpose, sometimes requiring pleurodesis to prevent recurrences.

Only a small proportion of pleural effusions are caused by drugs, which are usually associated with exudative-type pleural effusion. Early identification of this iatrogenic cause eliminates the need for further investigations, the treatment consisting in the cease of the incriminated medication. The drugs most commonly associated with this type of reaction are: procainamide, hydralazine, quinidine (drugs that induce lupus-like syndrome), nitrofurantoin, dantrolene, methysergide, procarbazine and methotrexate.

Diet

The restriction of lipid intake may be useful in the treatment of chylothorax, although this therapeutic method remains controversial. Repeated drainage of these pleural effusions can cause lymphopenia and rapid depletion of fat and protein deposits. Limiting oral fat intake may slow down the accumulation of chylous fluid in the pleura in some patients. Hyperalimentation or total parenteral nutrition may preserve the nutritional deposits, but this recommendation is restricted for patients whose underlying etiology may benefit from definitive therapy.

Pharmacological treatment

Pharmacological therapy for pleural effusions depends on the etiology of the underlying condition. For example, drug therapy includes nitrates and diuretics for congestive heart failure and pulmonary edema, antibiotics in the event of parapneumonic pleural effusion and empyema, or anticoagulants in the event of pulmonary embolism.

Antibiotic therapy should be initiated early when the presence of parapneumonic pleural effusion, empyema or pleural effusion associated with esophageal perforation or intra-abdominal

abscess are suspected. The selection of antibiotics should be made on the basis of the potential causative microorganisms and the clinical presentation. As there is a wide range of single or combined molecules, patients' age, comorbidities, disease duration, living conditions (institutionalized persons) and local sensitivity of microorganisms should be considered. The antimicrobial spectrum should generally cover anaerobic organisms. Therapeutic options include clindamycin, broad-spectrum penicillins, imipenem. Sometimes, depending on the clinical condition of the patient, the opinion of a specialist in infectious diseases is required.

Special attention should be given to the interactions between drugs, adverse effects and pre-existing pathology.

Vasodilators are used for their ability to decrease the pre-load. Nitroglycerin is a first-line therapy for patients who are not hypotensive, ensuring an excellent reduction in pre-load. Higher doses cause a slight reduction in the after-load. Nitroglycerin is a drug with rapid onset and short duration of action (both within a few minutes), ensuring a rapid clinical effect, but also a rapid discontinuation in adverse clinical situations.

Loop diuretics decrease plasma volume and edema by increasing diuresis. Furosemide increases the excretion of water through interference with the chloride-binding carrier system, which further inhibits the reabsorption of sodium and chlorine in the ascending Henle loop and distal renal tubule.

Anticoagulants are used in the treatment of current thrombembolic disorders or in the prevention of their recurrences, by inhibiting thrombogenesis. Heparin increases antithrombin III activity and prevents the conversion of fibrinogen to fibrin. It does not induce clot lysis, but may inhibit thrombogenesis. Heparin also prevents clot reaccumulation after spontaneous fibrinolysis.

Surgical treatment

Surgery is often indicated in parapneumonic effusions that cannot be adequately drained by small-bore catheters, and can be used for diagnostic as well as therapeutic purposes (e.g. for pleural sclerosis therapy in exudative pleural effusions).

Pleurodesis by insufflating the talc directly onto the pleural surface using video-assisted thoracoscopy is an alternative to using talc slurries.

Decortication is usually required when there are thick, rigid pleural peels that restrict ventilation and cause refractory or progressive dyspnea. Chronic, organizing parapneumonic pleural effusions require complex surgical maneuvers for drainage of the pleural fluid and obliteration of the pleural space.

Surgically implanted pleuroperitoneal shunts are another viable method of treatment for recurrent, symptomatic pleural effusions, usually in the context of a malignancy, but also in the therapeutic approach of chylous effusions. Over time, the shunts are prone to malfunction, requiring surgical revision and are poorly tolerated by patients.

Less often, surgery is necessary to close the diaphragmatic defects (thus preventing the repeated accumulation of pleural fluid in patients with ascites) or for ligation of the thoracic duct to prevent the reaccumulation of chylous effusions.

Therapeutic thoracentesis

Therapeutic thoracocentesis is a useful maneuver to evacuate a large amount of pleural fluid in order to relieve dyspnoea, and prevent inflammation and fibrous adhesions in the parapneumonic pleural effusions.

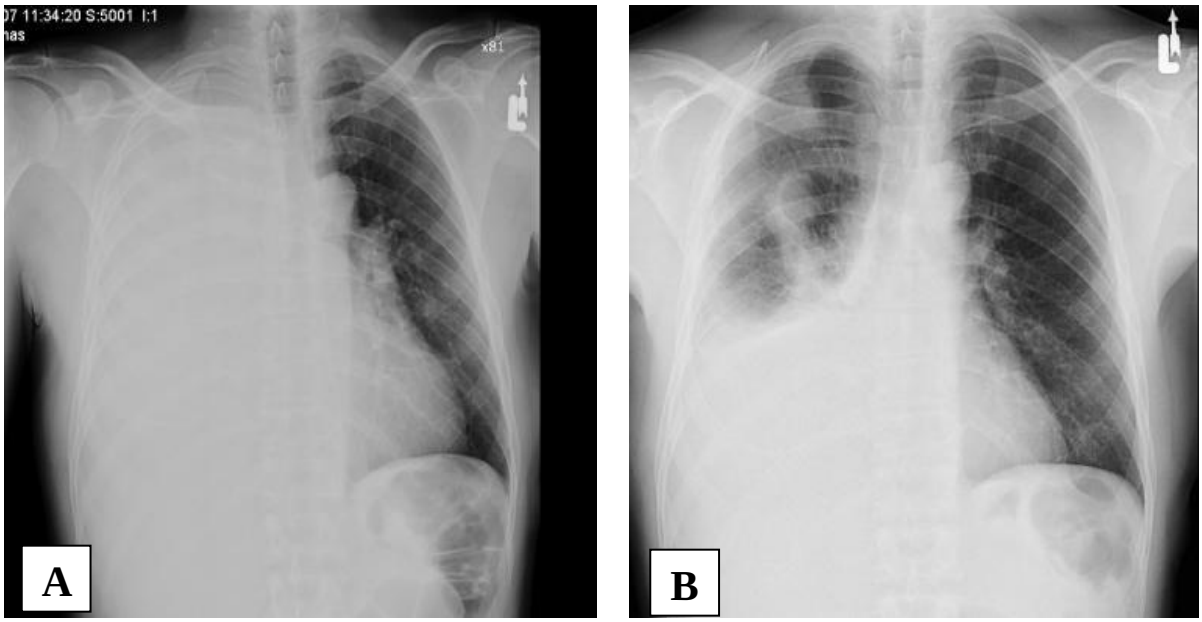


Fig. 3. A. Massive right pleural effusion with medistinal shift to the left. B. Right pleural effusion after partial drainage, with improvement of left mediastinal shift.

Although free parapneumonic effusions can usually be drained by therapeutic thoracentesis, complicated parapneumonic collections or empyema sometimes may require tube thoracostomy drainage.

Pleurodesis involves the instillation of an irritating agent in the pleural space in order to induce an inflammatory syndrome that leads to the creation of fibrous bridges between the parietal and visceral pleural membranes, thus obliterating the pleural space. Pleurodesis is most often used in recurrent pleural effusions of malignant etiology (pulmonary neoplasm, ovarian neoplasm or metastatic breast cancer).

Various agents, including talc, doxycycline, bleomycin sulfate (Blenoxane), zinc sulphate and quinacrine hydrochloride can be used for sclerosis of the pleural space and can effectively prevent recurrence of malignant pleural effusion.

Evolution and prognosis

The prognosis of pleural effusion varies with the underlying condition's etiology. However, early addressing in medical services, prompt diagnosis and adequate treatment result in a significant decrease in the complication rate.

Morbidity and mortality in pleural effusions are directly influenced by the cause of the generating disease (and its stage, where applicable) at the time of presentation, as well as by the result of biochemical tests in the pleural fluid.

Morbidity and mortality rates in patients with pneumonia and accompanying pleural effusion are higher than in patients with pneumonia alone. Parapneumonic pleural effusion, recognized and treated promptly, is usually resolved without significant sequelae. On the other

hand, in the absence of treatment or with inadequate treatment, the parapneumonic effusion may be complicated by constrictive pleural fibrosis, empyema and sepsis.

The development of a malignant pleural effusion is associated with reserved prognosis, with a median survival rate of 4 months and an average survival < 1 year. The most common malignancy in men is lung cancer, whereas in women is breast cancer. Median survival varies between 3 and 12 months, depending on the type of malignancy. Pleural effusions secondary to cancers that respond better to chemotherapy, such as lymphoma or breast cancer, are more likely to survive compared to pleural effusions secondary to lung cancer or malignant mesothelioma.

The results of the biochemical and cytological examination of the pleural fluid may also be prognostic indicators. For example, a lower pH of the pleural fluid is often associated with a higher tumor burden and a poorer prognosis.

Bibliography

1. Boka K, Soo Hoo GW, Rubins J. Drugs & Diseases. Pulmonology. Pleural effusions. https://emedicine.medscape.com (Updated: Dec 28, 2018)
2. Diaz-Guzman E, Dweik RA. Diagnosis and management of pleural effusions: a practical approach. *Compr Ther*. 2007 Winter. 33(4):237-46.
3. Sahn SA. Pleural effusions of extravascular origin. *Clin Chest Med*. 2006 Jun. 27(2):285-308.
4. Sahn SA. The value of pleural fluid analysis. *Am J Med Sci*. 2008 Jan. 335(1):7-15.
5. Noppen M. Normal volume and cellular contents of pleural fluid. *Curr Opin Pulm Med*. 2001 Jul. 7(4):180-2.
6. Sahn SA. The differential diagnosis of pleural effusions. West J Med. 1982 Aug. 137(2):99-108. [Full Text].
7. Light RW. The undiagnosed pleural effusion. *Clin Chest Med*. 2006 Jun. 27(2):309-19.
8. Culotta R, Taylor D. Diseases of the pleura. Ali J, Summer WR, Levitzky MG, eds. *Pulmonary Pathophysiology*. 2nd ed. New York: Lange Medical Books/McGraw-Hill; 2005. 194-212.
9. Askegard-Giesmann JR, Caniano DA, Kenney BD. Rare but serious complications of central line insertion. *Semin Pediatr Surg*. 2009 May. 18(2):73-83.
10. Heffner JE. Diagnosis and management of malignant pleural effusions. *Respirology*. 2008 Jan. 13(1):5-20.
11. Bouros D, Pneumatikos I, Tzouvelekis A. Pleural involvement in systemic autoimmune disorders. *Respiration*. 2008. 75(4):361-71.
12. Froudarakis ME. Diagnostic work-up of pleural effusions. *Respiration*. 2008. 75(1):4-13.
13. Wong CL, Holroyd-Leduc J, Straus SE. Does this patient have a pleural effusion? *JAMA*. 2009 Jan 21. 301(3):309-17.
14. Kalantri S, Joshi R, Lokhande T, Singh A, Morgan M, Colford JM Jr, et al. Accuracy and reliability of physical signs in the diagnosis of pleural effusion. *Respir Med*. 2007 Mar. 101(3):431-8.
15. Saraya T, Light RW, Takizawa H, Goto H. Black pleural effusion. *Am J Med*. 2013 Jul. 126(7):641.e1-6.
16. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med*. 1972 Oct. 77(4):507-13.
17. Light RW. Use of pleural fluid N-terminal-pro-brain natriuretic peptide and brain natriuretic peptide in diagnosing pleural effusion due to congestive heart failure. *Chest*. 2009 Sep. 136(3):656-8.
18. Menzies SM, Rahman NM, Wrightson JM, et al. Blood culture bottle culture of pleural fluid in pleural infection. *Thorax*. 2011 Aug. 66(8):658-62.
19. Sakuraba M, Masuda K, Hebisawa A, Sagara Y, Komatsu H. Pleural effusion adenosine deaminase (ADA) level and occult tuberculous pleurisy. *Ann Thorac Cardiovasc Surg*. 2009 Oct. 15(5):294-6.
20. Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions : an evidence-based guideline. *Chest*. 2000 Oct. 118(4):1158-71.
21. Zarogoulidis K, Zarogoulidis P, Darwiche K, et al. Malignant pleural effusion and algorithm management. *J Thorac Dis*. 2013 Sep. 5 Suppl 4:S413-9. [Full Text].
22. Efthymiou CA, Masudi T, Thorpe JA, Papagiannopoulos K. Malignant pleural effusion in the presence of trapped lung. Five-year experience of PleurX tunnelled catheters. *Interact Cardiovasc Thorac Surg*. 2009 Dec. 9(6):961-4.
23. Khaleeq G, Musani AI. Emerging paradigms in the management of malignant pleural effusions. *Respir Med*. 2008 Jul. 102(7):939-48.

13. LUNG CANCER

At present, worldwide, lung cancer is the most common cause of death through cancer. The mortality rate is higher in developed countries and is associated with tobacco consumption. Due to late diagnosis, only about 10% of patients can be treated curatively.

Risk factors

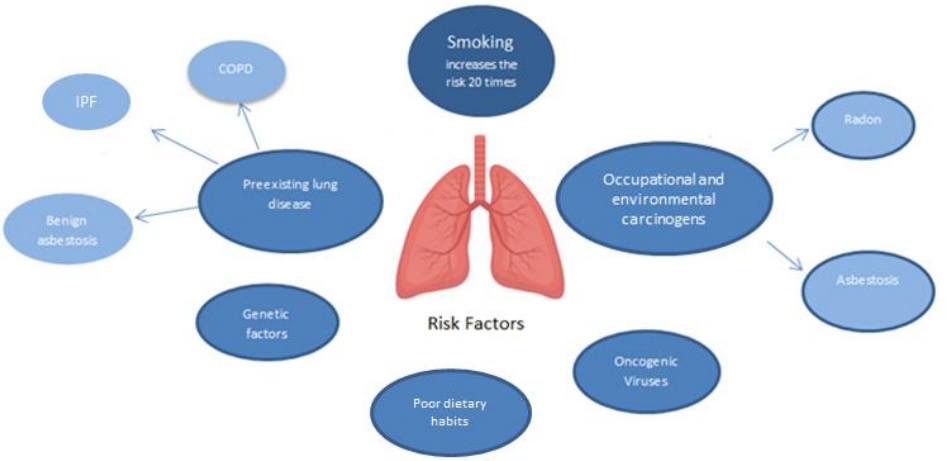


Figure 1. Risk factors for bronchopulmonary neoplasm

1. Smoking

Cigarette smoking is the most important risk factor in development of lung cancer. It is associated with approximately 80-90% of lung cancer deaths.

The composition of cigarette smoke is very complex. Only tar is made up of approximately 3500 compounds, most of which are carcinogenic. Moreover, even passive smokers have a significant risk of developing this neoplasm. It is considered that next to an active smoker who smokes 20 cigarettes, a passive smoker inhales the smoke from 8 cigarettes. Smoking cessation in people diagnosed with early-stage lung cancer has had beneficial prognostic results.

2. Genetic factors

The occurrence of this neoplasm among non-smokers with a family history of lung cancer, or young subjects without professional exposure, supports the hypothesis of a genetic determinism involved in the occurrence of this disease. Studies have shown that people with a family history of bronchopulmonary neoplasm have twice the risk of developing lung cancer compared with general population.

3. Professional exposure

Occupational exposure to carcinogens such as asbestos, radon, silicon, arsenic, beryllium, chloromethyl, ethers, chromium, nickel, cobalt or vinyl chloride increases the risk of lung cancer. Of these, asbestos is the first professional cause of lung cancer. Exposure to asbestos initiates carcinogenesis by inducing a chronic inflammatory response, and determining DNA mutations. Asbestos is also a major risk factor for the development of pleural mesothelioma.

4. Preexisting lung diseases

- COPD: Patients with airflow limitation are more prone to developing bronchopulmonary neoplasm.
- Interstitial lung disease
- Benign pulmonary asbestosis

5. Viral infections

Retroviral DNA and human papillomavirus DNA have been found in most cases of squamous cell carcinoma. Retroviral DNA has also been found in cases of adenocarcinoma.

6. Alimentation

Studies have shown a direct correlation between low fruit and vegetable consumption and an increased risk of bronchopulmonary neoplasm. Low serum concentrations of beta-carotene, vitamin A, C, E and selenium have been associated with development of lung cancer, these being protective substances with antioxidant effects.

7. Air pollution

Industrial pollution and exhaust gases of vehicles cause the release of carcinogenic micro-particles such as carbon monoxide (CO), polycyclic aromatic hydrocarbons, nitrogen dioxide (NO2), sulfur dioxide (SO2), benzene, ultrafine particles (PM 2.5um) into the atmosphere.

Carcinogenesis

The pathogenesis of bronchopulmonary cancer involves the accumulation of multiple molecular abnormalities over a long period of time. Between the period of exposure to the pollutants and the appearance of clinical manifestations, there can pass even decades. Carcinogens act on bronchial epithelium cells, leading to genetic mutations, with activation of promoter oncogenes and inactivation of tumor suppressor genes. In time, the initial cell, through successive mutations and the development of atypia, acquires malignancy. These cells will proliferate uncontrolled and will lead to the appearance of tissues with modified characters, called pre-invasive lesions: hyperplasia, dysplasia, metaplasia. Gradually, as pre-invasive lesions acquire the ability of invasion and metastasis, malignant lesions will appear.

Morphopathology

The evolution, prognosis and response to different types of treatment depend on the histopathological type of the tumors. These are divided into 2 major types: non small-cell carcinoma (non-microcellular) and small cell carcinoma (microcellular).

- **Squamous cell carcinoma** (epidermoid) accounts for about 35% of lung cancer cases. It is closely correlated to smoking. It occurs most commonly at the central level (large bronchi), usually having vegetative appearance. It invades deep the bronchial wall and

extends itself into the pulmonary parenchyma. It may obstruct the bronchus with onset of atelectasis or retrostatic pneumonia. Especially large tumors can associate central necrosis, which will appear as an excavated lession. Sometimes these tumors will be diagnosed as a result of an episode of hemoptysis that may be due to intratumoral haemorrhages or erosion by the tumor mass of the surrounding vascular walls. Metastases generally occur late.

- **Adenocarcinoma** represents about 40% of the cases of lung cancer and is more frequent in women and in non-smokers. It commonly develops in the peripheria, from the alveolar and bronchiolar epithelium. Local symptoms are more reduced than in centrall localized forms. Metastasizes lymphatically and hematogenously.

  Subtipes:

  a) Acinar
  b) Papilarlly
  c) Bronhioloalveolar
  d) Adenocarcinoma with solid mucid-forming
  e) Mixed histopathological types

- **Large cell carcinoma** accounts for approximately 15% of cancers, with usually peripheral localization, which can reach large sizes> 10cm
- **Small cell carcinoma** represents about 10-15% of CBP cases and is the most aggressive form, with rapid invasion of the mediastinum. The tumor mass generally appears central, with soft consistency, necrosis and bleeding. However, bronchial stenosis is late. It is commonly associated with para-neoplastic syndromes. Metastasizes early and multicentric (liver, brain, bone system), which leads to its discovery already in disseminated, inoperable form.

Clinical manifestations

Unfortunately, lung cancer symptoms may be nonspecific and variable, delaying diagnosis. The initial evaluation of the patient should include signs and symptoms related to the following:

a) Symptoms and signs determined by the primary tumor lesion

- *Cough* is one of the most common symptoms (90%) and is generally dry, persistent, and non-responsive to treatment. It occurs more frequently in central cancers. The underlying pathophysiological mechanisms are: irritation of nerve fibers, obstruction or bronchial compression, secondary infection, infiltration of the pleura. Although many smokers cough, lung cancer patients usually admit a change in their coughing character.
- *Chest pain* may be present in 25% -50% of patients at the time of presentation for lung cancer assessment. The pain tends to be deaf, persistent and stays at the same region. It occurs secondary to pleural / bone system invasion or mediastinal enlargement.
- *Hemoptysis* may be inaugural, variable in intensity and may be persistent or recurrent. This is due to the erosion of the vessels by the tumor.
- *Dyspnea* appears late and is more frequent in central forms.
- *Stridor* may reflect an endoluminal obstruction. It appears as a result of compression or obstruction of the trachea or large bronchi.
- *Secondary infections* occur as a result of obstruction of the bronchial lumen by the tumor process, with stagnation of secretions and infection, subsequently causing pneumonia or retrostenotic abscesses.

b) Symptoms and signs determined by intrathoracic dissemination of the tumor

- *Dysphonia* through compression / invasion of the recurrent laryngeal nerve;
- *Dysphagia* by compression / invasion of the esophagus;
- *Superior vena cava syndrome* includes a collection of signs and symptoms resulting from compression of the superior vena cava: upper body edema (upper chest, neck, face, arm), cyanosis, spider veins, headache, high blood pressure. The developing edema can cause functional deficiencies of the larynx or pharynx, contributing to cough, hoarseness, dyspnea and dysphagia.
- *Pancoast-Tobias syndrome* characterizes the signs and symptoms caused by an apical pulmonary neoplasm. It includes ribs erosion, arm and shoulder pain due to the invasion of the brachial plexus, the atrophy of the intrinsic hand muscles and the invasion of the cervical sympathetic with the onset of Claude-Bernard-Horner syndrome: miosis, eyelid ptosis, enophthalmia.
- *Ascension of the hemi-diaphragm* caused by phrenic nerve paralysis.
- *Pleural effusion* by direct invasion, with blockage of lymph node drainage and it is frequently a hemorrhagic effusion.
- *Pericarditis* by pericardial extension.
- *Coastal erosion* with their destruction.

c) Symptoms and signs determined by metastases

Lung cancer can metastasize to any organ. Patients with metastases often have nonspecific systemic symptoms: anorexia, weight loss or fatigue.

The most common areas of metastasis are the brain, liver, adrenal glands, bone system.

Liver metastases are often accompanied by symptoms of weakness and weight loss. Their presence is associated with a poor prognosis.

Bone metastases are accompanied by pain or fractures on the pathological bone. The ribcage and vertebral bodies are most commonly affected, but any bone may be involved.

Brain metastases: causes intracranial hypertension syndrome, confusion, personality disorders, seizures.

Paraneoplastic syndromes

Represent non-metastatic determinations of cancer. They are characterized by a tumoral secretion of hormones and peptides and may precede the tumor detection by several months. Disappear after treatment and can reappear in case of recurrence. They are most commonly associated with small cell carcinoma.

- *Endocrine* – hypercalcemia, Cushing's syndrome, Inadequate secretion of ADH with severe hyponatremia or inadequate secretion of ACTH
- *Bone - hypertrophic osteoarthropathy, digital hipocracy*
- *Neurological* - Eaton – Lambert syndrome (impairment of neuromuscular junction by pre-synaptic release of acetylcholine), sub-acute sensitive neuropathy, sub-acute cerebral degeneration
- *Hematological* - anemia, migratory thrombophlebitis, eosinophilia
- *Vasculitis* – polymyositis and dermatomyositis
- *Cutaneous* - Acanthosis nigricans
- *Renal* - glomerulonephritis, nephrotic syndrome

Paraclinical investigations

A. Imaging tests

Postero-anterior and lateral **chest X-Ray** are usually the first imaging tests performed by a patient who has symptoms. These can reveal (figures 1-4):

- Hilar opacity: homogeneous, with infiltrative outline. It can be given by the tumor or by hilar adenopathies.
- The solitary pulmonary nodule becomes evident from diameter of 1 cm. Homogeneous, well delimited.
- Parenchymal opacity of variable dimensions. Non-homogeneous, non-systematized, with an irregular outline or spicules.
- Cavitary lesion: has thick, irregular walls. It occurs through central necrosis of the lesion.
- Micro-nodular opacities: multiple, with blurred outline, subcostal intensity, uneven.
- Atelectasis: opacity of a certain extension, homogeneous, with a clear outline, retractable to the surrounding tissues (mediastinum, diaphragm)
- Condensation: occurring distally from bronchial obstruction
- Pleural effusion

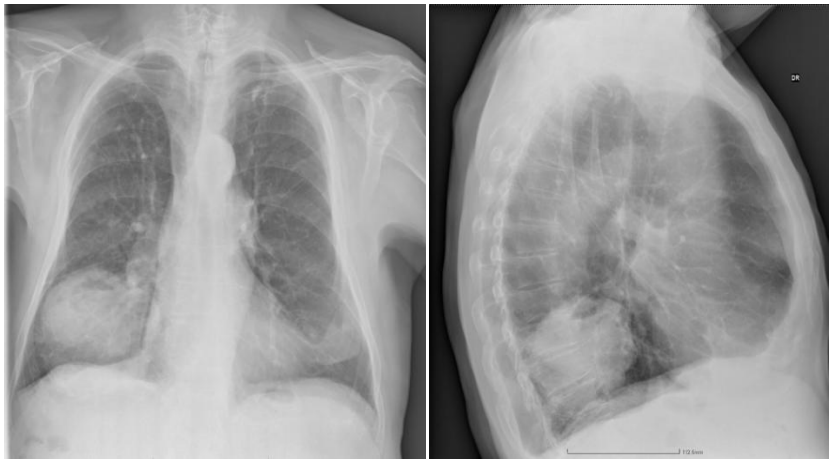


Figure 2. Peripheral lung cancer of the lower right lobe. Excavated macroopacity with a hyper-transparent area. The differential diagnosis is made with an abscess.

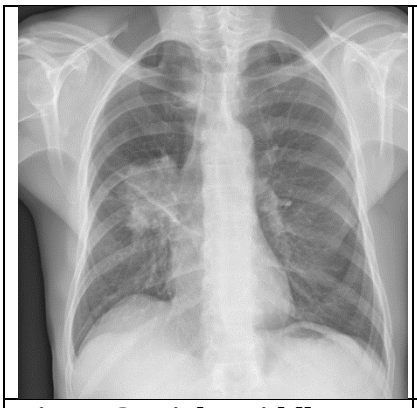
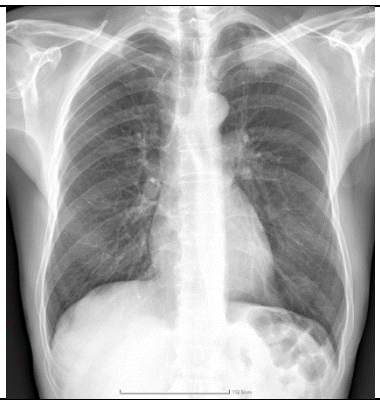
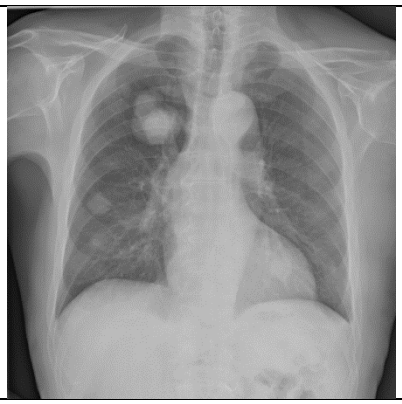
		

Figure 3. Right middle - pulmonary neoplasm. Macro-opacity with irregular contour and spikes	**Figure 4. Left apical macro-opacity. The differential diagnosis is made with pulmonary infiltrate from Mycobacterium Tuberculosis (MTB) infection.**	**Figure 5. Pulmonary metastasis. Multiple well-shaped nodular opacities, with right pulmonary and left retrocardiac pulmonary projection. The main differential diagnosis is made with uncomplicated pulmonary hydatid cysts.**

Contrast-enhanced Computed Tomography (CT) of the thoracic segment

A clinical presentation and a chest x-ray that raises the suspicion of a proliferative process, is an indication for performing a contrast-enhanced chest CT examination. This investigation is important for the exclusion of some differential diagnoses but also for the staging of lung cancer (localization, dimensions of primary tumor mass, detection of adenopathic masses or pulmonary/ pleural/ bone metastasis).

Positron emission tomography (PET-CT)

Is a modern imaging technique that detects intense metabolic activity of tumor cells. Uses a fluoride-labeled glucose molecule (18F) - fluorodeoxyglucose - abbreviated FDG. Scanning is not only for one segment, but for the whole body.

Magnetic resonance imaging (MRI) is used only for the evaluation of apical tumors with a possible invasion of the brachial plexus and for the evaluation of bone system invasion.

B. Histopathological cofirmation

Bronchoscopy with biopsy (see chapter 2).

A lung cancer diagnosis is mandatory confirmed by histopathological examination.

The following macroscopic aspects may be encountered in bronchoscopy:

- Endobronchial masses with vegetative, polylobate appearance, well-vascularized, with necrotic areas, which cause tracheal / bronchial obstruction.
- Neoplastic infiltration of the bronchial epithelium.
- Extrinsic compressions, without invasion of the bronchial epithelium caused by tumor masses or adenopathies that can lead to incomplete or complete tracheal / bronchial obstruction.

Direct visualization of the tumor, allows the bronchial biopsy to be performed, with the histopathological examination of the sample. Brushing and bronchial lavage with cytological examination, can be associated.

Modern bronchoscopic techniques allow sampling beyond the visual limit, through transbronchial biopsies performed under fluoroscopic control, or puncture and aspiration of lymph nodes, through transbronchial needle aspiration (TBNA) or bronchial echoendoscopy (EBUS-TBNA). These techniques allow the confirmation and staging of lung cancer.

Minimally invasive therapeutic maneuvers, with palliative purpose, such as endobronchial mass resection and bronchial stenting can also be performed through interventional bronchoscopy.

Cytological examination of sputum

It can be used as a screening method, but the sensitivity is low even if immunohistochemical stains are used.

Liquid biopsy

It is a noninvasive investigation, which is based on the detection of circulating tumor DNA, having extensive clinical utility and can act as a complementary method for tissue biopsies, for monitoring tumor recurrence or resistance to treatment.

Transthoracic biopsy is usually performed under ultrasound or CT guidance. It is a fast and relatively safe way to confirm the diagnosis of lung cancer.

Mediastinoscopy and thoracoscopy allow direct visualization of the affected hemithorax, biopsies and lung cancer staging by assessing adenopathies.

C. Tumor markers

They do not constitute screening / diagnostic methods in lung cancer, but can be used for therapeutic monitoring of lung cancer patients: CYFRA 21-1 (cytokeratin fragment 21-1), CEA (carcinoembryonic antigen), NSE (neuron specific enolase).

Differential diagnosis

a. Benign lung tumor

It is frequently asymptomatic, discovered incidentally following routine investigations.

Radiological: round / oval opacity with well-defined, homogeneous and with a slow dynamic.

b. Pneumonia

The onset is acute: fever, shivers, pleuritic chest pain, cough with mucopurulent expectoration, dyspnea ± myalgia, arthralgia etc. Radiologically, a condensation with aerial bronchogram, which respects the lung fissures. Paraclinically, leukocytosis with neutrophilia and increased systemic inflammation markers. Following the administration of antibiotic therapy, a resorption of the pneumonic process takes place.

c. Pulmonary Tuberculosis

The onset is insidious, dominated by general signs and symptoms (fatigability, marked weight loss, night sweats, low fever). Lung lesions have polymorphic appearance (infiltrative, nodular, cavitary lesions), predominantly located in the upper lobes and have a slow dynamic. Sputum examination is generally positive, Mycobacterium Tuberculosis being identified by

microscopic examination and / or culture. The lesions are slowly resorbing / fibrosis following the administration of the anti-tuberculosis treatment.

d. Pulmonary abscess

Similar onset as in pneumonia with general symptomes, asthenia, anorexia, fever, cough with fetid expectoration, chest pain, sometimes hemoptysis. Radiologically in the formation phase, a homogeneous round/oval opacity, with blurred contour, is highlighted. In the suppuration phase, a cavity image with thick walls and hydro-aerial level appears. Paraclinically associates leukocytosis with neutrophilia and increased inflammation markers. Following the administration of antibiotic therapy, the slow resorption of the abscess takes place.

e. Hydatid cyst

It manifests through dry, irritant cough, progressive dyspnea, chest pain. The rupture of the cyst results in the externalization of its contents with the expectoration of a clear liquid (hydatid vomiting). Radiologically, one or more round, oval, homogeneous and variable-sized opacities can be detected. Frequently it associates hepatic cysts and Ac. anti-Echinococcus tapeworm are present in biological examination.

f. Bronopneumonia (differential diagnosis with pulmonary metastases)

The onset is acute with fever, shivers, malaise. Radiologically, multiple opacities of variable sizes, located bilaterally and asymmetrically. Paraclinic: leukocytosis with neutrophilia and increased inflammatory markers. The clinical and paraclinical parameters normalize under antibiotic treatment.

Performance status assessment

Performance index: evaluated on the ECOG scale or through the Karnovsky Index.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

(Adapted from Guide for Lung Cancer management)

Karnovsky Index- 100 indicates perfect health and 0 represents death	
Normal no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs or symptoms of disease	90
Normal activity with effort; some signs or symptomps of disease	80
Cares for self; unable to carry on normal activity or to do active work	70
Requires occasional assistance,but is able to care for most of his personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severly disabled; hospital admission is indicated although death not imminent	30
Very sick; hospital admission necessary; active supportive treatment necessary	20
Moribound; fatal processes progressing rapidly	10
Dead	0

(Adapted from Guide for Lung Cancer management)

Staging

TNM staging with the 3 components that describe the anatomical extension of the tumor: T-extension and size of the primitive tumor, N- lymph node involvement, M- secondary determinations.

T-primary tumor	
Tx	The presence of malignant cells in the sputum or in the bronchoalveolar lavage, without highlighting the tumor from an imaging or bronchoscopic point of view.
T0	Without evidence of primary tumor
Tis	Carcinoma in situ
T1	Dimensiunea tumorii ≤ 3cm
T2	Tumor size 3 - 5 cm
T3	Tumor size 5 - 7 cm
T4	Tumor size> 7cm
N- lymph node involvement	
Nx	the lymph nodes cannot be visualized
N0	without lymph node metastases
N1	metastases in the peribronchial ipsilateral lymph nodes and / or in the hilarious lymph nodes
N2	metastases in the mediastinal ipsilateral lymph nodes or subcarinal lymph nodes
N3	metastases in the mediastinal or hilly controlateral lymphatic lymph nodes or in the scalp or supraclavicular ipsilateral / control lymph nodes
M- distant metastases	
M0	No distant metastases
M1	Present metastases

Classification of Small Cell Lung Carcinoma

Limited stage: a hemithorax, mediastin, ipsilateral supraclavicular adenopathy, without pleural effusion.

Extended stage: beyond the limited stage of the disease.

Treatment

Treatment, especially of the non-small cell type (NSCLC), has made significant progress, following the results of the fundamental research, which were reflected in the prediction of response to treatment and the development of targeted therapies. The treatment is prescribed according to the histological type, the stage of the disease, the associated conditions and prognosis. This includes surgery, chemotherapy, radiotherapy, targeted molecular therapy and immunotherapy, for curative or palliative purposes.

In recent years, certain genetic mutations have been discovered in pulmonary adenocarcinomas: activating mutations of EGFR (epidermal growth factor receptor, present in about 10% of patients) or rearrangements of the ALK gene (anaplastic lymphoma kinase, present in about 4% of patients).Targeted molecular therapy with anti-EGFR tyrosine kinase inhibitors (Erlotinib, Gefitinib, Afatinib) and inhibitors of ALK (Crizotinib, Ceritinib) as well as immunotherapy (Nivolumab, Pembrolizumab) have increased survival in those with metastatic disease.

Treatment of non-microcellular cancers

Stage I-II

The elective treatment with curative purpose is the *surgical* one. The intervention is preceded by an extended pulmonary functional evaluation, to estimate the postoperative pulmonary function and possible complications. The surgical procedures depends on the extent of the disease, performance status, respiratory function tests and cardiovascular status.

Adjuvant cytostatic treatment (cisplatin + vinorelbine, cisplatin + etoposide) improves 5-year survival. Radiation therapy is indicated in stage I NSCLC in patients with surgical contraindication or who refuse the intervention.

Stage III

Neoadjuvant chemotherapy benefits in stage III NSCLC, and cytostatic combinations are similar to adjuvants.

Adjuvant radiotherapy is indicated in incomplete resected NSCLC or stage IIIA-N2.

Neoadjuvant chemoradiotherapy is a therapeutic option in potentially resectable local advanced NSCLC.

Stage IV

For patients with non-squamous NSCLC, Bevacizumab (monoclonal anti-VEGF antibody) may be combined with chemotherapy. Another option for patients with advanced disease, recurrent or metastatic disease, with EGFR mutations or with ALK rearrangements, there are the EGFR tyrosine kinase inhibitors and ALK inhibitors. If patients have progression of the disease under chemotherapy, immunotherapy may be used.

Palliation is intended for those who do not respond to any of the lines mentioned above, and aims to improve the quality of life.

Treatment of microcellular cancers

Limited disease stage: etoposide/platinum based chemotherapy (cisplatin or carboplatin). Early concomitant chemotherapy with radiotherapy is superior to sequential therapy.

Extended stage of disease: The recommended treatment is chemotherapy (etoposide / cisplatin or etoposide / carboplatin) and if a remission of the neoplasm is found, then it will be followed by prophylactic cranial irradiation. Palliation is intended for those who do not respond to chemoradiotherapy.

Minimally invasive therapies:

- In the case of symptomatic obstruction of the airways, endoscopic debulking ± stent placement may be performed;
- For superior vena cava syndrome, vascular stents can be placed;
- Recurrent pleural effusions can be treated by pleurodesis, with sclerosing agents such as talc powder.

Prognosis

Despite therapeutic innovations, survival in lung cancer remains poor: 15% for all stages. It is superior for patients with curative surgery.

Prognostic factors for inoperable stages are: ECOG / Karnovsky performance index, presence of symptomatology at diagnosis and histopathological type.

Bibliography

1. Akhtar N, Bansal JG. Current Problems in Cancer 2017
2. Anwar A, Jafri F, Ashraf S, Jafri MAS, Fanucchi M. Paraneoplastic syndromes in lung cancer and their management. 2019(e)ko ;7(15):1–9.
3. Baker S, Dahele M, Lagerwaard FJ, Senan S. A critical review of recent developments in radiotherapy for non-small cell lung cancer. Radiat Oncol 2016
4. Corrales L, Scilla K, Caglevic C, Miller K, Oliveira J, Rolfo C. Immunotherapy in Lung Cancer: A New Age in Cancer Treatment. 65–95 or.
5. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, et al. Non-small-cell lung cancer. 2015(e)ko;1:1–16.
6. Guidelines ECP. Clinical and Organizational Factors in 3rd ed: American College of Chest Physicians. 2013(e)ko ;(May):121–41.
7. Hinton J, Cerra-franco A, Shiue K, Shea L, Aaron V, Billows G, et al. Superior vena cava syndrome in a patient with locally advanced lung cancer with good response to definitive chemoradiation: a case report. J Med Case Rep 2018(e)ko ;1–6.
8. Hofman P. Liquid biopsy for early detection of lung cancer. 2017(e)ko ;73–8.
9. Hoseok I, Cho J. Lung Cancer Biomarkers 1. arg. Advances in Clinical Chemistry. Elsevier Inc.; 2015. 1–64 or
10. Tudorache PDV. Curs de pneumologie. Romania: Voicu Tudorache;
11. Robert J. Mason, Arthur Slutsy, John F.Murray Jay A. Nadel, Michael Gotway Robert, MURRAY & NADEL'S TEXTBOOK OF RESPIRATORY MEDICINE, SIXTH EDITION. 2015(e)ko ;6.
12. Jones JH, Li A, Smith SK, Roy L, Fras AM. Conservative Management of Neuropathic Pain in a Patient With Pancoast-Tobias Syndrome: 2018(e)ko ;11(2):29–31.
13. Juan MMO, Reguart AIN, Carcereny JMTE, Campelo RG. SEOM clinical guidelines for the treatment of non‐small cell lung cancer (2018). Clin Transl Oncol 2019(e)ko ;21(1):3–17.
14. Pi C, Zhang M, Peng X, Zhang Y, Xu C, Zhou Q. Liquid biopsy in non-small cell lung cancer: a key role in the future of personalized medicine? 2017(e)ko ;0(0).
15. Pulmonar C. Ghid pentru managementul cancerului pulmonar. 2015
16. Ruysscher D De, Popat S, Peters S, Felip E, Group GW. clinical practice guidelines clinical practice guidelines. 2013(e)ko ;21(February 2002):1–7.
17. Schil PE Van, Hellmann MD, Peters S, Guidelines E. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.
18. Tumors L, Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, et al. The 2015 World Health Organization Classification Journal of Thoracic Oncology [2015(e)ko ;10(9):1243–60.
19. Waqar SN, Morgensztern D. SC. Pharmacogy and Therapeutics [Internet]. 2017

14. SLEEP DISORDERED BREATHING

There are 3 major conditions

- Obstructive sleep apnea syndrom (OSAS);
- Central sleep apnea syndrome (CSAS) and Cheynne – Stokes respiration;
- Obesity – hypoventilation syndrome (OHS).

Obstructive sleep apnea syndrom (OSAS)

1. **Definition**

OSAS is represented by repeated episodes of respiratory total (apneas) or partial (hypopneas) collapse during sleep, with of duration of more than 10 seconds, and a number of more than 5/h of sleep, associated with micro-arousals and >3% oxygen desaturation.

2. **Epidemiology**

OSAS has a prevalence of 10-17% in males, 3-9% in females, 2-3% in children and 25-30 % of profesional drivers.

3. **Pathogenesis, risk factors, etiology**

Pathophysiology is multifactorial. Contributing factors are: narrowed airways with high colapsability during sleep; airway respiratory muscles with inadequate response and low tonus; increased microarousal treshold at respiratory disturbances; hypersensitive respiratory control of breathing.

Obesity is a major contributing factor due to obstruction of upper airways, with local fat deposition and lipid infiltration of the tong.

Retrognatia, micrognatia, mandibular hypoplasia, macroglosia, tonsil hypertrophy, inferior movement of hyoid bone, uvula hypertrophy can lead to narrowing of upper airway caliber. Nasal polips, septum deviation and nasal congestion can aggravate OSAS.

Patients with OSAS have an increasesd risk of systemic hypertension, stroke, miocardial infarction, with increased cardiovascular morbidity and mortality. OSAS is associated with insulin resistance, diabetes, metabolic syndrome, and untreated patients have an increased risk of traphic accidents.

4. **Clinical features**

Tipical patient is overwight/obese, with heavy snoring, nicturia, chocking and reported apneas during sleep, excessive daytime somnolence, mild cognitive disfunction, and frequent cardio – metabolic diseases. Symptoms develop in years, progresively with weight increased, aging and menopause. Diagnostic of OSAS is a combination of clinical symptoms and an objective sleep study.

Nightime symptoms: reported apneas, chocking, unrefreshed sleep, enurezis, nocturnal sweats, nasal congestion, hipersalivation, gastro-esofageal reflux, erectile disfuntion.

Daytime symptomes: excessive somnolence, astenia, dry mouth, morning headache, atention deficit, iritability, mood changee.

Excesive daytime somnolence

Somnolence is a common symptom. During an obstructive apnea, the patient progresivelly increases respiratory effort in order to open the obstructive airways, with a micro-

awakening. Repeated microarousals lead to fragmented sleep, with a decreased REM and N3 sleep. Symptoms progresses gradualy and many patients are not aware of their problems, until their activities and performances are severly afected. Only ¼ of OSAS patients have somnolence as the main symptom, while ~ 50% have fatigue and astenia as most significant symptoms. Many patients underestimate the severity of sleepiness. Beacause there is a 2-3 time increased risk of trafic accidents, somnolence is very important for the diagnostic and evaluation of severity of OSAS.

Obesity

Obesity is one of the most important risk factor for OSAS. 70% of patients with body mass index (BMI) $\geq$ 40 kg/m^2 have OSAS. Fat deposition at the neck level is found also in patients with normal BMI. Neck circumference of > 43 cm in males and of > 41 cm in females is a significant risk factor.

Evaluation of somnolence:

1) subjective with standardised questionnaire (ex. Epworth Sleepiness Scale, Stanford Scale);

2) reaction time test for standard activities (ex. Trail Making Test, Mackworth Clock Test and Psychomotor Vigilance Test);

3) electroencephalography (EEG) – for sleep latency and/or ability to stay awake in certain conditions (ex. Multiple Sleep Latency Test (MSLT), Maintenance of Wakefulness Test (MWT).

Epworth Sleepiness Scale (ESS)

ESS measures the probability of falling asleep during specific daily activities. The questionnaire has 8 questions. A score of $\geq$10 of 24 points defines a clinical relevant somnolence.

5. **Pozitive diagnostic**

Diagnostic of OSAS:

a. Evaluation of symptoms: a. Diurnal symptoms; b. Nocturnal symptoms

b. Medical history and investigation: a.Comorbidities; b.Medication; c.Physical evaluation; d. Diadnostic tests (blood pressure, ECG, blood gases, etc).

c. Specific tests: a.Diurnal functional tests; b.Full night polisomnography

OSAS – Diagnostic criteria ICSD-2 (AASM 2005)

A. At least one: 1. Episod of unintentioned sleep during wakefullness, excesive daytime somnolence, unrefreshed sleep, fatigue or insomnia; 2. Awakenings with sensation of chocking, apnea; 3. Reported heavy snoring, apnea, or both.

B. PSG: 1. $\geq$5 respiratory events (apnea, hypopnea, or RERAs)/h of sleep; 2. Presence of respiratory effort during respiratory events. OR

C. PSG : 1. $\geq$15 respiratory events (apnea, hypopnea,or RERAs)/h of sleep; 2. Presence of respiratory effort during respiratory events.

D. The condition can not be explained by other sleep disturbances, medical or neurological diseases, medication, drugs.

Classification

There are 3 main respiratory events during sleep:

1. Obstructive apnea, the most frequent. Severity of OSAS is measured based o the number of apnea-hypopnea events/h of sleep (AHI): MILD: 5-14/h; MODERATE: 15-29/h; SEVERE: over 30/h.

2. Central apnea, with the lack of respiratory effort when the brain does not send the signal. Can be: idiopatic (CSAS primar); secundary: Cheyne-Stokes respiration (in heart failure, stroke), periodic respiration at high altitude, drugs.

There are 2 types of CSAS : a.Hipercapnic or alveolar hypoventilation – secondary to central alteration of respiration or in diseases of respiratory muscles.

b.Eucapnic or Hipocapnic - associated with Cheyne-Stokes respiration from heart failure and/or other vascular diseases.

Cheyne-Stokes respiration: ≥ 5 central apnea/hyponea/h with symptoms; it coexists with mixed apnea/hypopnea, over 50% central; pattern crescendo-descrescendo +/- central events.

3. Mixed apneea, a combination of obstructive and centrale apneas.

Complex apnea is the persistance of central events after the remision of obstructive apneas with CPAP/BiPAP. Remission of obstructive apneas lead to hyperventilation with Hering-Breuer reflex, followed by limitation of a certain level of thoracic expansion. Prevalence estimated is 10%. Treatment is with assisted servo-ventilation (ASV).

Nocturnal polisomnography

Objective evaluation with a sleep study, usind 4 levels of devices, according to number of sensors and the presence or absence of a sleep technician.

1. Standard PSG, full-night, video- assisted: minimum 7 channels of EEG, EOG, EMG, ECG/HR, respiratory flux, respirator effort, SaO2.

2. PSG in laboratory, full night, unassisted: minim 7 canale, EEG, EOG, MG, ECG/FC, flux, respiratory effort, SaO2.

3. Poligraphy (PG) 4-8 channels: minim 4, respiratory flux, respirator effort, HR, SaO2.

4. 1-3 chanals: SaO2, HR and/or respiratory flux.

6. **Treatment**

For obese patients, weight reduction is a strong reccomendation. The gold standard is nasal continuos positive airway pressure during sleep (nCPAP).

6.1. Devices for mandibular advancement (oral devices)

These customized oral devices anvance mandibula, increasing the area of upper airways at the hypopharinx level, improving OSAS. They can be monobloc (one piece) or duobloc (two pieces) and are reccomended for mild to moderate OSAS or for severe patients with limited tolerance at CPAP. 65% of patients have a 50% reduction of AHI. Oral devices reduce snoring, excessive somnolence, with some positive impact on cardiovascular risk and cognitive function.

6.2 Surgery

Conservative surgical ENT interventions are indicated for a limited number of patients with the goal of increasing the volume of the upper airways and reduction of closure pression.

Uvulo-palato-pharingoplasty (U3P) has a limited use because of irreversible side effects. The purpose on intervention is to shortened the uvula, decreasing the dimension of the soft palate

and tonsil removal. More conservative interventions are reccomended such as laser uvula remmodeling, nasal septum surgery, resection at the mucosal level.

Osteotomy with maxilo-mandibular advancement has the purpose of anterior repositioning of the mandibula, enlarginf the retropalatal and retro lingual spaces. It is rarely used, in specialised centers, mostly for congenital micro-retrognatia with minimal response and intolerance at CPAP.

Adenotonsilectomy it the first line of treatment in children with OSAS and large tonsils and nasal polips.

Electrical stimulation of genioglosus muscle with a implatable pacemaker is a new method, useful in a higly selected group of patients, but expensive, and available only in few centers in the world, with modest results.

Bariatric surgery in indicated in morbid obesity (BMI over 40kg/m^2). Diferrent technics are used: gastric sleave, gastric baloon, bypass. More than 50% of patients have significant improvement, but many still need CPAP.

6.3 Continuos positive airway pressure during sleep (nCPAP)

CPAP is the most efficient treatment for OSAS. Room air is pumped through the mask at the nose or nose and mouth level with adjusted positive pressure during sleep. These devices are computerised minicompresors, with memory cards, allowingt to follow – up patients at regular interval or by tele-medicine. The positive pressure prevents the colapse of the upper airways muscles during sleep.

CPAP reduces daytime somnolence and sleep fragmentation, improving neuro-cognitive functions, atention and learning. CPAP improves metabolic syndrom, reduces insulin resistance, lowering levels of TNF- alfa, IL-6, C reactive proteine.

CPAP reduces heart rate variability and sistemic blood pressure.

Adherence to CPAP remains a problem, compliance rate is 50-60% at one year, reducing the therapeutic effect, many patients remaining wth increased risk of developing cardiovascular comorbidities.

6.4 Medication

Some drugs were tested: protriptilin (antidepresiv), paroxetină (serotonin reuptake inhibitor), mirtazapin (serotonin receptor antagonist), teofilin (anticolinergic), but with no significant results. Actazolamide is efficient in the treatment of some form of CSAS with fluid retention, but has no effect on OSAS.

Bibliography

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002; 165: 1217–1239.
2. Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med 2001; 164: 2147–2165.
3. Hedner J, Bengtsson-Bostrom K, Peker Y, et al. Hypertension prevalence in obstructive sleep apnoea and sex: a population-based case–control study. Eur Respir J 2006; 27: 564–570.
4. Arzt M, Young T, Finn L, et al. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med 2005; 172: 1447–1451.
5. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnea–hypopnea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005; 365: 1046–1053.
6. Rodenstein D. Sleep apnea: traffic and occupational accidents – individual risks, socioeconomic and legal implications. Respiration 2009; 78: 241–248.
7. Engleman MH, Douglas NJ. Sleep. 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. Thorax 2004; 59: 618–622.
8. McNicholas WT. Diagnosis of obstructive sleep apnea in adults. Proc Am Thorac Soc 2008; 5: 154–160.
9. American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd Edn. Westchester, American Academy of Sleep Medicine, 2005.
10. Phillips B, Naughton MT. Clinical presentation. In: Phillips B, Naughton MT, eds. Obstructive Sleep Apnea. Oxford, Health Press, 2004.
11. Young T, Hutton R, Finn L, et al. The gender bias in sleep apnea diagnosis: are women missed because they have different symptoms? Arch Intern Med 1996; 156: 2445–2451.
12. Engleman HM, Hirst WS, Douglas NJ. Underreporting of sleepiness and driving impairment in patients with sleep apnoea/hypopnoea syndrome. J Sleep Res 1997; 6: 272–275.
13. Hein H. Objectifying sleepiness. In: Randerath SJ, Sanner BM, Somers VK, eds. Sleep Apnea. Prog Respir Res. Basle, Karger, 2006; 35: pp. 43–46.
14. Peppard PE, Young T, Palta M, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 2000; 284: 3015–3021.
15. Flemons WW, McNicholas WT. Clinical prediction of the sleep apnea syndrome. Sleep Med Rev 1997; 1: 19–32.
16. P Palange, A.K Simonds, Respiratory Medicine 2nd Edition- ERS handbook, editors P Palange, A.K Simonds, European Respiratory Society 2013.
17. Fischer J, Dogas Z, Bassetti CL, Berg S, Grote L, Jennum P, Levy P, Mihaicuta S, Nobili L, Riemann D, Puertas Cuesta FJ, Raschke F, Skene DJ, Stanley N, Pevernagie D; Executive Committee (EC) of the Assembly of the National Sleep Societies (ANSS); Board of the European Sleep Research Society (ESRS), Regensburg, Germany. J Sleep Res. 2012 Aug;21(4):357-68.
18. Mihaicuta S, GroteL. Clinical picture and diagnosis- in Sleep Medicine Textbook, Editors – in Chief: Claudio Bassetti, Zoran Dogas, Philippe Peigneux, pag 233-250, European Sleep Research Society 2014.
19. Randerath W, Bassetti CL, Bonsignore MR, Farre R, Ferini-Strambi L, Grote L, Hedner J, Kohler M, Martinez-Garcia MA, Mihaicuta S, Montserrat J, Pepin JL, Pevernagie D, Pizza F, Polo O, Riha R, Ryan S, Verbraecken J, McNicholas WT.Challenges and perspectives in obstructive sleep apnoea: Report by an ad hoc working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society. Eur Respir J. 2018 Sep 16;52(3).

15. IDIOPATHIC PULMONARY FIBROSIS

Interstitial lung diseases (ILDs) comprise a heterogeneous group of lung diseases involving the distal lung parenchyma, generating varying degrees of inflammation, fibrosis and architectural distortion. Although the interstitium is the primary site of injury, these disorders frequently affect also the airspaces, peripheral airways, and vessels along with their respective epithelial and endothelial linings.

There are described over 200 entities, most of them rare diseases, which generate an extremely wide spectrum of pathological, clinical and radiological features, with a considerable overlap. Because there may be dramatic prognostic and therapeutic differences between these entities, accurate diagnosis is essential for patient management.

The most organized and systematic diagnostic approach uses the classification of the International Consensus adopted by the American Thoracic Society / European Respiratory Society in 2013 (Figure 1).

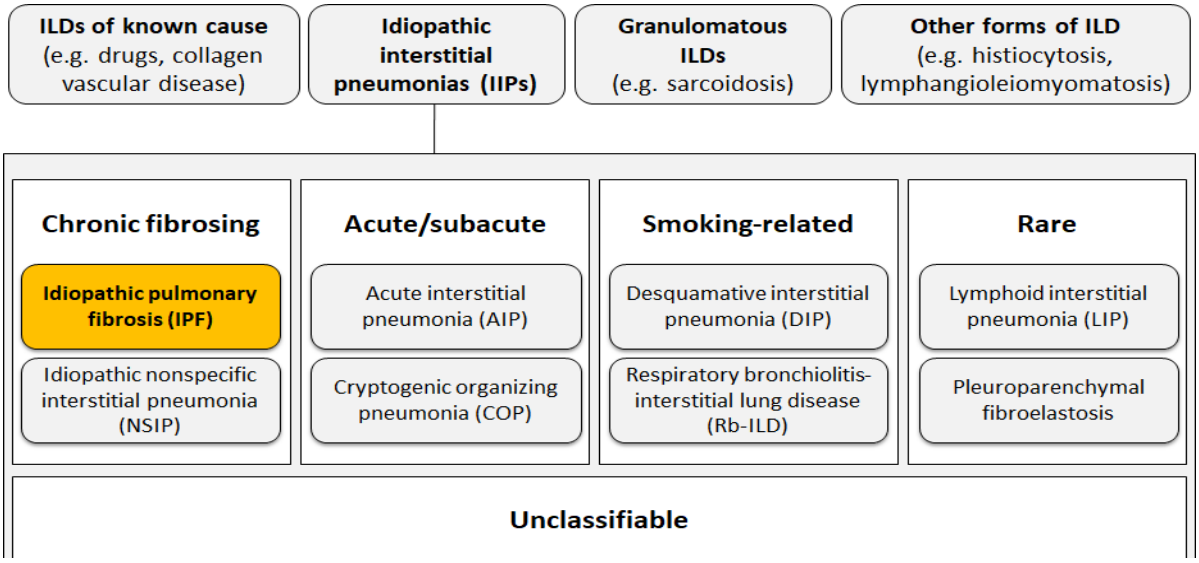


Figure 1. Classification of interstitial lung diseases (ILDs)

Idiopathic pulmonary fibrosis (IPF)

IPF is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It occurs primarily in older adults, is limited to the lungs, and is defined by the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). It is characterized by progressive dyspnea and declining lung function. IPF is associated with a poor prognosis. Patients have a median survival of 3.5 years from the time of diagnosis.

IPF is considered a rare disease (occurring in less than 5 per 10000 person-years). It should be considered in all adult patients (over 50 years) with insidious and subacute onset shortness of breath on exertion, dry cough and bibasilar inspiratory Velcro crackles. Finger clubbing may be present.

Male gender and cigarette smoking are risk factors for IPF. A number of environmental associations have been identified, including metal dusts, wood dusts, stone/sand, and exposure to livestock.

Different genetic alterations have been associated with an increased risk of IPF, such as shortened telomeres, oxidative injury, surfactant dysfunction, proteostatic dysregulation, endoplasmic reticulum stress, mitochondrial dysfunction leading to decreased alveolar epithelial cell proliferation and the secretion of profibrotic mediators.

The current model for the pathogenesis of IPF consists of repeated injury of the alveolar epithelial cell that leads to aberrant epithelial activation that generates a profibrotic environment. Once the profibrotic pathway is stimulated, activated fibroblasts differentiate into myofibroblasts and cause excessive extracellular matrix deposition, leading to remodeling of the lungs with a "honeycomb" appearance (Figure 2).

The stages involved in the initiation and progression of fibrosis are:

a) the onset of fibrosis is characterized by repeated subclinical injuries (autoimmunity, viruses, particles, cigarette smoke) that generate alveolar epithelial damage and destruction of the alveolar capillary basement membrane;

b) this process is followed by defective reepithelialization, myofibroblastic proliferation and formation of the extracellular matrix;

c) processes of repair by apoptosis and phagocytosis of mesenchymal cells are dysfunctional, resulting in excessive accumulation of extracellular matrix with progressive remodeling and pulmonary destruction.

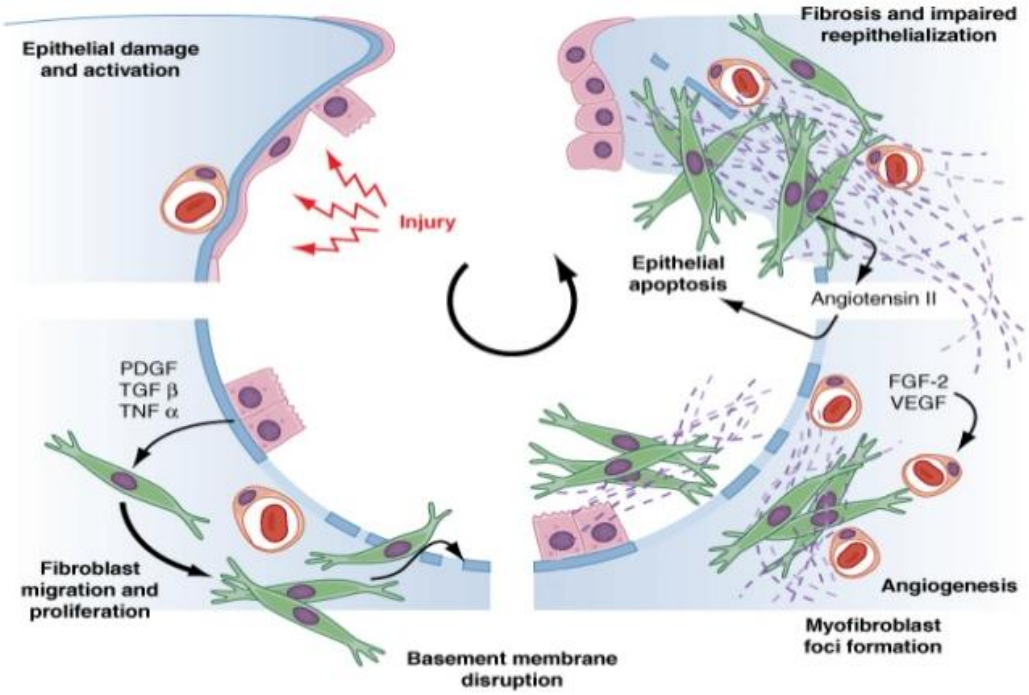


Figure 2. Pathogenic stages in the development of pulmonary fibrosis

The histological pattern regarded as representing clinical IPF is usual interstitial pneumonia (UIP). The cardinal findings of UIP include: geographic and temporal heterogeneity (alternating zones of normal and abnormal lung), predilection for peripheral (subpleural) and basilar regions, fibroblastic foci (aggregates of proliferating fibroblasts and myofibroblasts), excessive collagen and extracellular matrix and honeycomb change.

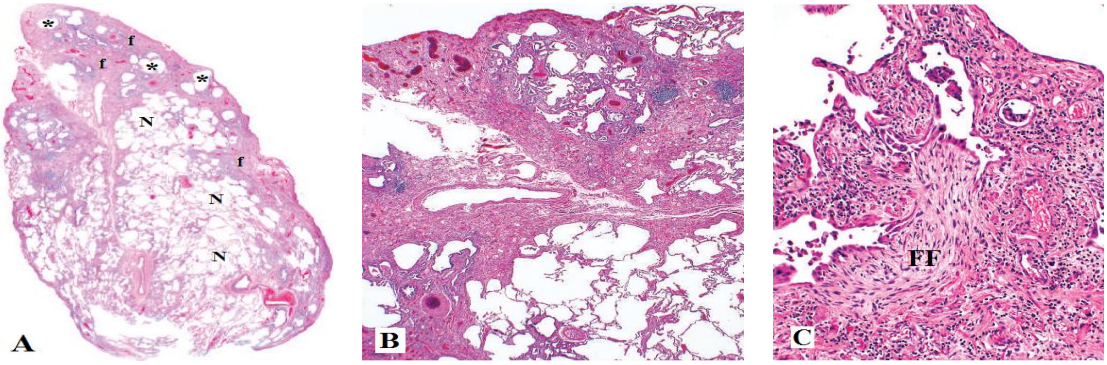


Figure 1. Histopathology demonstrating usual interstitial pneumonia (UIP) A. Heterogeneous areas of dense fibrosis (f) andmicroscopic cysts (*) interspersed with areas of relatively normal lung architecture (N). B. C. Fibroblast foci (FF): areas of extracellular matrix and fibroblasts.

UIP can also be encountered in other ILDs including connective tissue diseases, chronic hypersensitivity pneumonitis, drug toxicity, and asbestosis (through chronic inflammatory mechanisms that induce severe pulmonary structural changes). However, the clinical (prognostic) significance of UIP within these entities differs significantly compared to IPF. Thus, in these situations the histopathological pattern should be considered UIP-like, in order to differentiate the idiopathic UIP generated by the specific pathogenic mechanisms of IPF.

Radiographic manifestations of IPF.

Chest radiographs in IPF typically reveal diffuse, bilateral interstitial or reticulonodular infiltrates, with a predilection for basilar and peripheral (subpleural) regions. Thin section high-resolution computed tomographic (HRCT) scans are invaluable to diagnose IPF as can assess the nature and extent of parenchymal abnormalities. UIP is the hallmark radiologic pattern of IPF. Cardinal features of UIP include: heterogeneous, "patchy" involvement; predilection for peripheral (subpleural) and basilar regions; honeycombing; coarse reticular opacities (interlobular and intralobular septal lines); traction bronchiectasis or bronchioloectasis. Honeycombing is a distinguishing feature of UIP and must be present for a definite HRCT diagnosis of UIP to be made. Honeycombing refers to clustered cystic airspaces of typically consistent diameter (3–10 mm, but occasionally larger) with thick, well-defined walls.

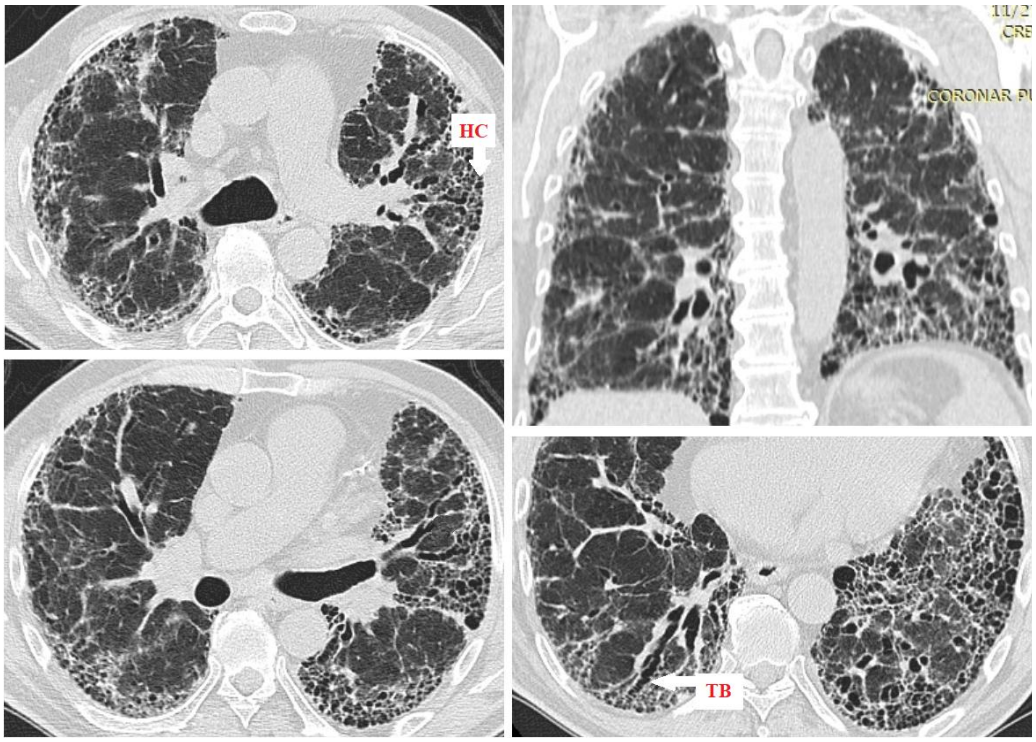


Figure 4. HRCT images demonstrating a UIP pattern
Honeycombing (HC) with peripheral tractionbronchiectasis (BT)

The diagnostic algorithm for FPI is shown in Figure 5. Exclusion of known causes of pulmonary fibrosis is a key factor in the diagnostic process. Even in the presence of the HRCT or histopathological UIP pattern, the definitive diagnosis requires exclusion of chronic hypersensitivity pneumonitis, connective tissue diseases, drug toxicity or asbestosis, these entities being able to mimic IPF. Diagnostic confidence is increased through multidisciplinary discussion (MDD) between pneumologists, radiologists and pathologists experienced in ILDs diagnosis.

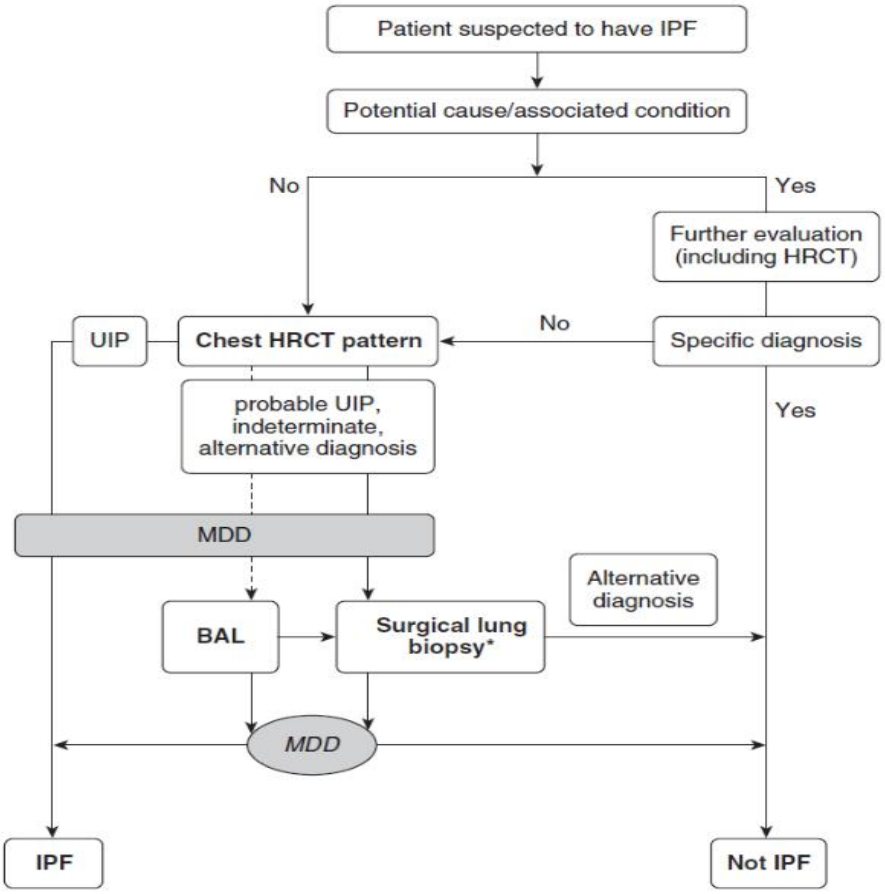


Figure 5. Diagnostic algorithm for IPF

A restrictive ventilatory defect (reduced TLCand FVC; increased FEV1/FVC ratio) in association with a reduction in Dlcois characteristically seen in IPF. Pulmonary function tests accurately reflect the histological severity of the disease, being superior to the imaging evaluation or symptomatology. Thus, it is the most sensitive method of quantifying the severity of IPF at diagnosis. At the same time, pulmonary functional assessment offers the most standardized approach for objective quantification of disease progression. Significant change that is indicative of disease progression is defined as a 10% change inFVC or a 15% change in DLco, from baseline values.

Clinical disease courses in patients with IPF

There are several possible disease courses in patients with IPF. Patients may experience rapid disease progression or a much more gradual progression of disease, while some patients exhibit periods of relative stability punctuated by periods of acute worsening. The typical natural history of IPF is the slow progression of the disease with a median survival period of approximately 3 years from thet ime of diagnosis. In some cases, abrupt and rapid deteriorations, triggered by unidentifiable causes or obvious causes, occur during the chronic clinical course. The deteriorationis termed an acute exacerbation of IPF and is associated with significant morbidity and mortality.

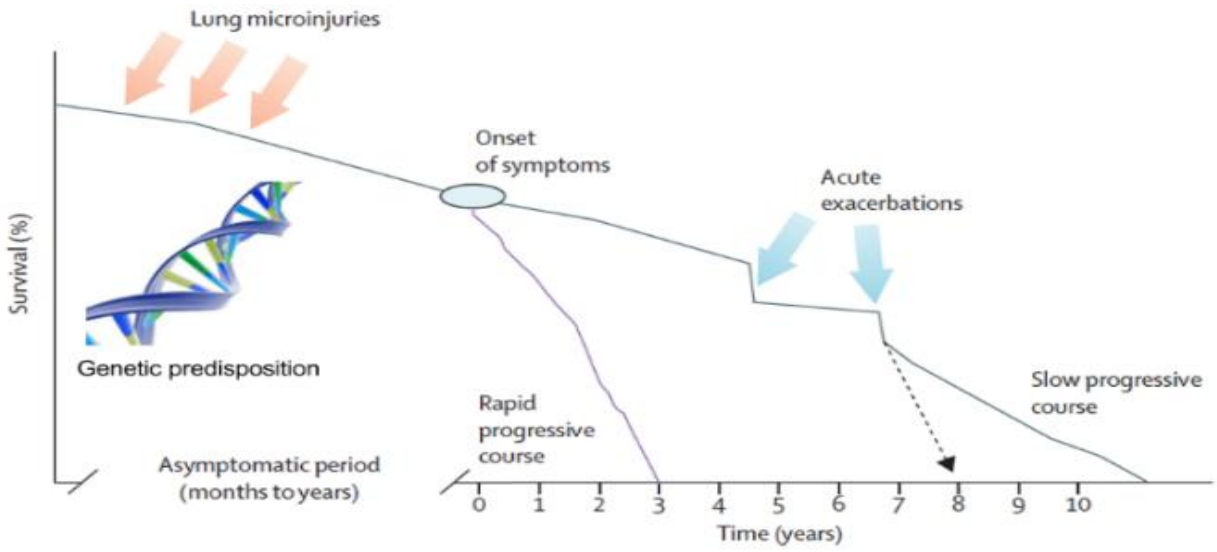


Figure 6. Natural history of IPF

Treatment of IPF

Currently, there is no curative treatment for IPF. The main aim of treatment is to relieve the symptoms as much as possible and slow down its progression. As the condition becomes more advanced, end of life (palliative) care will be offered.

Pharmacotherapy of IPF

Two molecules, pirfenidone (antifibrotic agent) and nintedanib (tyrosine kinase inhibitor), have shown similar efficacy in reducing the rate of decline of lung function and prolonging survival of IPF patients.

Pirfenidone has been shown to have antiinflammatory and antifibrotic properties, but the exact mechanism of action in IPF is not completely understood. Pirfenidone suppresses the activity of multiple proinflammatory cytokines and TNF-α, and inhibits TGF-β with downstream reduction of fibroblast proliferation. Randomized studies have shown that pirfenidone significantly reduced FVC decline. Pirfenidone also significantly reduced the decline in 6-minute walk test (6MWT) distance and reduced disease progression, defined as an absolute decrease in FVC% predicted of ≥10% and/or a decrease in 6MWT distance of ≥50 m or death by 43% compared with placebo.

Nintedanib is a potent tyrosine kinase inhibitor with a distinct specificity targeting growth factors involved in fibrotic changes in the lungs of patients with IPF. Compared with placebo, treatment with nintedanib demonstrated a significant decrease in the rate of decline of lung function as measured by FVC. Furthermore, treated patients had greater time to an acute exacerbation and a reduction in both all-cause and respiratory-specific mortality.

Treatment should be individualized after careful discussion with the patient about the outcome of the therapy and the potential adverse effects of the drugs. Both drugs can cause significant gastrointestinal symptoms. Diarrhea is a common adverse effect of nintedanib, while nausea, dyspepsia, and vomiting have been observed more frequently in pirfenidone. Pirfenidone may cause photosensitivity and rash upon exposure to direct sunlight.

Non-pharmacological management for IPF

Exercise-induced hypoxemia is a major factor limiting exercise tolerance in IPF. Night hypoxemia is also common, having a negative impact on quality of life. Although there is little evidence for survival benefits, long-term oxygen therapy (LTOT) is recommended for patients with significant resting hypoxemia (indirect evidence from COPD patients).

Pulmonary rehabilitation improves exercise capacity and helps to cope with functional activities of daily life in IPF patients, even though the significance of these benefits is smaller and lasts for less time than in other chronic lung disease like COPD. Thus, because in patients with IPF the effects of pulmonary rehabilitation diminish rapidly, physical training should be part of the patient's daily routine.

Pulmonary rehabilitation may include anti-smoking counseling, psychosocial assistance, symptomatology and exacerbation management, prevention and management of respiratory infections, nutritional counseling, preparation for lung transplant and post-transplant rehabilitation.

Lung transplantation is the only option for patients with rapid progression and high risk of death in the following two years without transplantation. The average post-transplant survival for patients with IPF is estimated at 4.5 years.

Although there is no clear data to guide the timing of transplantation, criteria based on the degree of respiratory functional deterioration and identification of the rapidly progressive phenotype have been proposed. Thus, lung transplantation should be considered in the presence of HRCT or histopathological evidence of UIP pattern and one of the following: DLco <39% of predicted, CVF decrease >10% in the last 6 months, desaturation <88% at 6MWT, extension of honeycombs changes >50% of lung parenchyma.

Bibliography:

1. Raghu G, Remy-Jardin M, Myers JL, et al. *Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline*. Am J Respir Crit Care Med, 2018.
2. Steven D Nathan, A Whitney Brown, Christopher S King. *Guide to Clinical Management of Idiopathic Pulmonary Fibrosis*.Adis; 1st ed. 2016 edition.
3. Nakamura, Hiroyuki, Aoshiba, Kazutetsu. *Idiopathic Pulmonary Fibrosis. Advances in Diagnostic Tools and Disease Management*. Springer Japan 2016.
4. Travis WD, Costabel U, Hansell DM, et al. *An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias*. Am J Respir Crit Care Med, 2013.
5. Robert P. Baughman, Roland M. du Bois. *Diffuse Lung Disease. A Practical Approach*.Springer-Verlag New York 2012.

16. PULMONARY INVOLVEMENT IN CONNECTIVE TISSUE DISEASES

Connective tissue disease refers to a group of disorders involving the protein-rich tissue that supports organs. Connective tissue has a structural role and is found everywhere in the body. The causes of chronic auto-aggression are unknown and current therapies are not curative. More than 80 autoimmune diseases, 100 types of arthritis, 200 disorders of connective tissue and 3000 skin disorders are currently described. Lung involvement is found more common in rheumatoid arthritis, systemic lupus erythematosus and scleroderma (and rarely in dermatomyositis, polyarteritis nodosa, ankylosing spondylitis etc).

Rheumatoid Arthritis

Definition. Rheumatoid arthritis (RA) is a chronic inflammatory disease with autoimmune pathogenesis, characterized by a deforming and destructive arthropathy along with multiple systemic manifestations. The exact cause of RA is not known, but the onset of the disease appears to be the result of the interaction between genetic susceptibility and environmental triggers.

Incidence. RA is one of the most common autoimmune disorders, affecting about 1-2% of the population worldwide. The overall prevalence of the disease was estimated to be 0.24%, being about 2 times higher in women, with a maximum incidence between 35-50 years.

Clinical manifestations. RA is characterized by progressive lesions of the joints associated with various peri and extra-articular manifestations. Joint involvement is the characteristic feature of RA. In general, the small joints of the hands and feet are affected in a relatively symmetric distribution. In decreasing frequency, the metacarpophalangeal, wrist, proximal interphalangeal, knee, metatarsophalangeal, shoulder, ankle, cervical spine, hip, elbow, and temporomandibular joints are most commonly affected. The joint and periarticular lesions are characterized by the swelling of the joints and the sensitivity to palpation, with morning rigidity and limiting movement in the joints involved. The insidious onset of pain with symmetrical swelling of the small joints is characteristic. Although any joint may be affected, distal interphalangeal, sacroiliac joints and lumbar spine are rarely involved. Typically, clinical symptoms are most obvious in the morning, with joint stiffness lasting at least one hour. This is a subjective sign and the patient must be carefully informed about the difference between pain and stiffness. The pain, fatigue and deformities associated with rheumatoid arthritis result in a significant impairment on the quality of life.

Severe asthenia, weight loss, dyspnoea, are common clinical signs that may be associated with extra-articular manifestations. Thus, may accur ocular manifestations (irritation, iridocyclitis, scleritis, scleromalacia perforans, keratoconjunctivitis), renal manifestations (mesangial / membranous glomerulonephritis more often without clinical expression, renal amyloidosis, iatrogenic complications (gold salts, D-penicillamine, cyclosporine, NSAIDs)), cardiac manifestations (pericarditis, arrhythmias, valvulopathies), vascular impairment (Raynaud's syndrome, rheumatoid vasculitis), muscular manifestations (inflammatory myositis, muscular atrophy in the vicinity of the affected joints induced by prolonged joint rest, or some medications such as cortisone, antimalarials).

Table 1 – Pulmonary manifestations of rheumatoid arthritis

1. Pleural effusion	• uni or bilateral; more common in men and in chronic disease • pleural fluid is a clear serocitrin exudate, with high RF and LDH, low complement and low glucose levels • favorable course with corticotherapy
2. Rheumatoid nodules	• single or multiple macro-nodular opacities • asymptomatic • can become infected, or may rupture in the pleura causing pneumothorax • Caplan syndrome: occurs only in patients with both RA and pneumoconiosis related to mining dust (coal, asbestos, silica).
3. Interstitial lung disease +/- Vascular disease (Rheumatoid vasculitis, Pulmonary hypertension)	• clinically manifested by progressive inspiratory dyspnoea, chronic cough • generates restrictive respiratory dysfunction • radiographic features (HRCT): peripheral basilar predominant reticular abnormalities, honeycombing, traction bronchiectasis, and minimal to no ground-glass opacification

Lung damage can be iatrogenically induced as a result of RA treatment (Methotrexate may induce fibrosis or pancytopenia with consequent infection). Approximately 30% to 40% of patients with RA develop impaired respiratory function. The severity of pulmonary impairment is not associated with rheumatological symptoms or disease duration, but it reduces the survival. Although RA is more common in women, lung disease occurs more frequently in men with chronic disease, positive rheumatoid factor and subcutaneous nodules. Pleural involvement, usually asymptomatic, is the most common manifestation of lung disease and may occur concomitantly with pulmonary nodules or interstitial lung disease.

Diagnostic studies. Laboratory studies typically reveals a chronic inflammatory syndrome with increased ESR (in flares) and CRP (the most accurate inflammation test in RA). The ESR and the CRP level are associated with disease activity. The CBC commonly demonstrates anemia of chronic disease and correlates with disease activity. Immunologic parameters include autoantibodies (eg, RF, anti-CCP antibodies). RF is not specific for RA but is also present in other connective tissue diseases, infections, and autoimmune disorders, as well as in 1-5% of healthy people. X-ray reveals osteo-articular erosions and/or joint osteopenia. Chest radiography/HRCT may detect interstitial lung disease, rheumatoid nodules, pleurisy. Articular ultrasound is useful to evaluate synovitis, bone erosions. Spirometry is useful to monitor the restrictive ventilatory dysfunction, and DL_{CO} the alteration of the gas transfer through the alveolo-capillary membrane. In some cases, complex investigations such as MRI, scintigraphy, echocardiography, cardiac catheterization etc, are required.

Diagnostic criteria. Polyarticular involvement and abnormal values of systemic inflammatory tests are the most typical features that suggest RA, but a confident diagnosis is often difficult.

Table 2 - 1987 Rheumatoid Arthritis Classification (American College of Rheumatology)

Nr.	Criterion
1	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are rightor left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4	Simultaneous involvement of the same joint areas (as defined in 2) on both sides fo the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has beenpositive in <5% of normal control subjects
7	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)
For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made.	

Studies have shown that the 1987 ACR criteria are suboptimal when identifying subjects with early RA. In 2010, new ACR / EULAR criteria for classification of RA were developed, which take into account the articular impairment, serology (presence and title of RF and anti-CCP antibodies), duration of synovitis (under or over 6 weeks) and acute phase reactants (ESR, CRP). The evaluation of RA activity is performed by calculating the disease activity score (DAS), which is currently used to evaluate the effectiveness of remission therapy.

Differential diagnosis of RA

Table 3 – The main conditions that need to be considered in the differential diagnosis of RA

Infections	Viral (e.g. dengue, human immunodeficiency virus – HIV, parvovirus, cytomegalovirus, hepatitis), bacterial (e.g. N. gonorrhoeae, S. aureus), microbacterial, fungal, and others
Spondyloarthritis	Reactive arthritis (Chlamydia, Salmonella, Shigella, Yersinia), ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis
Systemic rheumatic diseases	Systemic lupus erythematosus, polymyositis/dermatomyositis, systemic sclerosis, Sjögren's syndrome, Behçet's disease, rheumatic polymyalgia, systemic vasculitis, and others
Microcrystalline arthritis	Gout, calcium pyrophosphate deposition disease, and others
Endocrine diseases	Hypothyroidism, hyperthyroidism
Neoplastic diseases	Metastatic neoplastic disease, lymphoma, paraneoplastic syndromes, and others
Others	Osteoarthritis, haemochromatosis, amyloidosis, sarcoidosis, serum sickness

The treatment is complex and interdisciplinary, adapted to the severity of the disease, complications and pathologies frequently associated. It includes: hygienic-dietary regimen, drug treatment, orthopedic and surgical treatment, kinetotherapy, physiotherapy, electrotherapy, occupational therapy. The hygienic-dietary regime generally recommends the avoidance of vicious positions, diet rich in vitamins, oligoelements, omega-3 and omega-6 polyunsaturated fatty acids, salt restriction diet (cortisone, NSAIDs), resting during acute exacerbations in functional position to reduce joint pain and combating muscle contracture. The drug treatment is complex, with multiple associations (see table 4).

Evolution, complications and prognosis. The clinical course of RA is generally one of exacerbations and remissions. Approximately 40% of patients become disabled after 10 years, but outcomes are highly variable. Some patients experience a relatively self-limited disease, whereas others have a chronic progressive illness. Common complications in RA are: infections (immunodepression), sudden death (atlantoaxial dislocation), renal amyloidosis, vasculitic complications and treatment induced. Predicting the long-term course of an individual case of RA at the outset remains difficult, though the following all correlate with an unfavorable prognosis in terms of joint damage and disability: high serum titer of autoantibodies, extra-articular manifestations, large number of involved joints, age younger than 30 years, female sex, systemic symptoms, insidious onset. Positive response to treatment indicates a better prognosis. The life expectancy of patients with RA is reduced by 5 to 10 years. Untreated patients have double mortality compared to people not affected by the same age. Common causes of death are cardiovascular disease (33-50% of all deaths) and infections (which are associated with about 25% of deaths). Also, it is known that RA is associated with higher risks for lymphoma, anemia, osteoporosis and depression.

Table 4 – The main therapeutic agents used in RA / collagenosis

Short-acting, fast-acting drugs	- NSAIDs, analgesics - corticosteroids administered locally or generally	Side effects: • digestive tract • kidney • cardiovascular • etc. Risk factors: old age, history of ulcer (± H. pylori), concomitant use of cortisone and anticoagulants, thrombocytopenia / platelet abnormalities, pregnancy, heart failure / cirrhosis / renal failure, asthma / nasal polyposis, allergies etc.
Slow-acting drugs that can induce remission	- Synthetic antimalarials - Gold salts - D-penicillamine - Salazopyrin - Methotrexate - Leflunomide - Cyclophosphamide - Azathioprine - Cyclosporine A	
Biologic agents	- Anti-TNF-α (Ac) antibodies o Infliximab (Remicade) o Adalimumab (Humira) o Etanercept (Enbrel) - Anti-IL1 antibodies - Anakinra - Anti-CD20 antibodies - Rituximab - Anti-IL6 antibodies - Tocilizumab - Anti T activators - Abatacept	

Systemic lupus erythematosus

Definition. Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by antibodies to nuclear and cytoplasmic antigens, multisystem inflammation, protean clinical manifestations, and a relapsing and remitting course. More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, epigenetic, ethnic, immunoregulatory, hormonal, and environmental factors (sun exposure, drugs, infections such as Epstein-Barr virus).

Epidemiology. Estimates of the annual incidence of SLE have ranged from approximately 1 to 10 per 100.000 population, while the prevalence of SLE has been estimated to range from approximately 5.8 to 130 per 100.000 population. The frequency of SLE varies by race and ethnicity, with higher rates reported in blacks and Hispanics.

Clinical manifestations. The classic presentation of a triad of fever, joint pain, and malar rash in a woman of childbearing age should prompt investigation into the diagnosis of SLE. However, patients may present with any of the following types of manifestations: constitutional, musculoskeletal, dermatologic, renal (nephritis), neuropsychiatric, pulmonary, gastrointestinal, cardiovascular (Raynaud's syndrome, valvulopathies, pericarditis, myocarditis), hematologic (anemia and thrombocytopenia).

SLE may lead to multiple pulmonary complications, including pleurisy, pleural effusion, pneumonitis, pulmonary hypertension, and interstitial lung disease. Pleurisy is the most common form of pulmonary disease in SLE, described in 30-50% of patients. The pleural effusion is exudative, usually small, uni or bilateral. Acute pneumonitis manifests with dyspnoea, cough, fever, hemoptysis, being difficult to differentiate from embolism or infection and having high mortality. Chronic pneumonitis or pulmonary fibrosis require careful radiological (HRCT) and functional (DL_{CO}) evaluation. Bronchiolitis obliterans with organizing pneumonia (BOOP) responds to corticotherapy, but is difficult to diagnose, sometimes requiring lung biopsy. Alveolar hemorrhage, although rare, is associated with antiphospholipid syndrome and has a high mortality rate. Pulmonary hypertension is often accompanied by Raynaud's syndrome. Pulmonary embolism may also be associated with antiphospholipid syndrome. Pulmonary infections are caused by immune abnormalities, but also by chornic steroid and immunosuppressive therapy. Tuberculosis and Pneumocystis carinii pneumonia are the most frequent infections in SLE. Shrinking lung syndrome is a restrictive ventilatory disorder, probably due to diaphragm dysfunction.

Diagnostic studies

Standard laboratory studies that are diagnostically useful when SLE is suspected should include: complete blood count (CBC) with differential, serum creatinine, urinalysis with microscopy, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), complement levels, liver function tests, creatine kinase assay, spot protein/spot creatinine ratio and special immunological tests (table 5). Depending on the affected organs, chest X-ray/HRCT, spirometry, DL_{CO}, echocardiography, cardiac catheterization etc, will be required.

Table 5 - Autoantibody Tests for SLE

ANA	Screening test; sensitivity 95%; not diagnostic without clinical features
Anti-dsDNA	High specificity; sensitivity only 70%; level is variable based on disease activity
Anti-Sm	Most specific antibody for SLE; only 30-40% sensitivity
Anti-SSA (Ro) or Anti-SSB (La)	Present in 15% of patients with SLE and other connective-tissue diseases such as Sjögren syndrome; associated with neonatal lupus
Anti-ribosomal P	Uncommon antibodies that may correlate with risk for CNS disease, including increased hazards of psychosis in a large inception cohort, although the exact role in clinical diagnosis is debated
Anti-RNP	Included with anti-Sm, SSA, and SSB in the ENA profile; may indicate mixed connective-tissue disease with overlap SLE, scleroderma, and myositis
Anticardiolipin	IgG/IgM variants measured with ELISA are among the antiphospholipid antibodies used to screen for antiphospholipid antibody syndrome and pertinent in SLE diagnosis
Lupus anticoagulant	Multiple tests (eg, direct Russell viper venom test) to screen for inhibitors in the clotting cascade in antiphospholipid antibody syndrome
Direct Coombs test	Coombs test–positive anemia to denote antibodies on RBCs
Anti-histone	Drug-induced lupus ANA antibodies are often of this type (eg, with procainamide or hydralazine; p-ANCA–positive in minocycline-induced drug-induced lupus)
ANA = antinuclear antibody; CNS = central nervous system; ds-DNA = double-stranded DNA; ELISA = enzyme-linked immunoassay; ENA = extractable nuclear antigen; Ig = immunoglobulin; p-ANCA = perinuclear antineutrophil cytoplasmic antibody; RBCs = red blood cells; RNP = ribonucleic protein; SLE = systemic lupus erythematosus; Sm = Smith; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.	

Diagnosis. As SLE has clinical and paraclinical polymorphism, diagnostic criteria are required (ACR / EULAR 2018 - table 6). SLE patients should score at least 10 points and all patients should have a serum anti-nuclear antibody (ANA) titer of at least 1:80 (HEp2 cells). If patients have more than one criteria in a single area, only the best-scoring criteria will be taken into account.

Differential diagnosis - table 4.

Evolution, complications, prognosis. The evolution is undulating with periods of remission and exacerbation. Complications occur as a result of the disease or therapies used. SLE is considered a risk factor with major impact in the onset of myocardial infarction. High-dose corticosteroids can cause infections (important cause of morbidity and mortality), diabetes, psychosis, osteoporosis, cataracts, sd. Cushing's, dyslipidemia. Early diagnosis and modern therapies have significantly improved the long-term prognosis in SLE, but it continues to have a significant risk of morbidity and mortality.

Treatment. The treatment objectives in SLE are the management of acute life-threatening episodes, the reduction of the risk of acute exacerbation during relatively stable periods, the improvement of the quality of life and the minimization of the therapeutic adverse effects. Nonsteroidal anti-inflammatories and hydroxychloroquine are used in the milder forms of the disease, corticosteroids and immunosuppressive therapy are reserved for patients with

involvement of vital organs, and anti-CD20 monoclonal antibodies for patients with severe forms, resistant to conventional therapy.

Table 6 – SLE diagnostic criteria (2018 ACR/EULAR)

Clinical Domains	**Criteria**	**Points**
Constitutional	Fever	2
Mucocutaneous	Non-scarring alopecia	2
	Oral ulcers	2
	Subacute cutaneous or discoid lupus	4
	Acute cutaneous lupus	6
Musculoskeletal	Joint involvement	6
Neuropsychiatric	Delirium	2
	Psychosis	3
	Seizure	5
Serosal	Pleural or pericardial effusion	5
	Acute pericarditis	6
Hematologic	Leukopenia	3
	Thrombocytopenia	4
	Autoimmune hemolysis	4
Renal	Proteinuria > 0.5 g/24 h	4
	Renal biopsy class II or V lupus nephritis	8
	Renal biopsy class III or IV lupus nephritis	10
Immunological domains	**Criteria**	**Points**
Antiphospholipid antibodies Complement proteins SLE-specific antibodies	Anti-cardiolipin antibodies or Anti-β2GP1 antibodies or Lupus anticoagulant	2
	Low C3 or low C4 Low C3 and low C4	3 4
	Anti-dsDNA antibody or Anti-Smith antibody	6

Systemic sclerosis

Definition. Systemic sclerosis is a chronic autoimmune disease of still not fully understood pathogenesis. Fibrosis, vascular wall damage, and disturbances of innate and acquired immune responses with autoantibody production are prominent features.

Incidence. Systemic sclerosis is a rare disease. Systemic sclerosis is estimated to occur in 2.3-10 people per 1 million. Overall, a substantial female predominance exists, with a female-to-male ratio of 3-6:1. Systemic sclerosis usually appears in women aged 30-40 years, and it occurs in slightly older men. In approximately 85% of cases, systemic sclerosis develops in individuals aged 20-60 years. There are 2.5 million people worldwide with scleroderma.

Clinical manifestations are caused by vascular damage and extensive tissue fibrosis, the main lesions involving the skin and internal organs (lung, digestive tract, heart and kidneys). Raynaud phenomenon, or whitening of the hands on exposure to cold, is a common finding. Pain in the affected digits, blanching, cyanosis, and hyperemia can follow. Difficulty in swallowing solid foods can be followed by difficulty with swallowing liquids and subsequent nausea, vomiting, weight loss, abdominal cramps, blotting diarrhea, and fecal incontinence.

Pulmonary involvement is suggested by the onset of inspiratory dyspnea, chest constriction, cough, sometimes hemoptysis, asthenia, intolerance to exertion etc. (table 7). The presence of interstitial lung disease (ILD) and/or pulmonary arterial hypertension (PAH) significantly worsen the prognosis of scleroderma patients. In the presence of PAH and/or digital ulcer, specific vasodilatory therapy with endothelin receptor antagonist (bosentan, macitentan), in addition to immunosuppressive therapy, is recommended. In severe cases, when chronic respiratory failure is present, complex therapeutic measures are required: cardiovascular support (diuretics, cardiotonic agents, calcium blockers, antiaggregants, anticoagulants etc) and respiratory support (long-term oxygen therapy, mucolytics etc).

Table 7 – Pulmonary involvement in systemic sclerosis

The two most common types of direct pulmonary involvement are:	Other possible pulmonary complications:
1. Interstitial lung disease / ILD 2. Pulmonary arterial hypertension / PAH	- aspiration, infection, drug toxicity, malignancy, respiratory muscle weakness, restrictive lung disease from chest wall involvement, lung disease secondary to cardiac involvement

Table 8 – Criteria for the classification of systemic sclerosis (SSc) / 2013 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)
Patients with a total score of ≥ 9 are classified as having definite SSc.

Item		Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)		9
Skin thickening of the fingers (only count the higher score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Interstitial lung disease	2
	Pulmonary arterial hypertension	2
Raynaud's phenomenon		3
SSc - related autoantibodies (maximum score is 3)	Anticentromere	3
	Anti-topoizomerase I	3
	Anti-RNA polymerase III	3

Key learnings:

- Connective tissue diseases requires interdisciplinary management.
- The lungs are frequently affected, both directly and through the therapeutic induced complications.
- Prognosis is poor in the presence of lung involvement.
- Athough the management is complex, it is not curative. Achieving disease remission, prevention of osteo-articular damage and systemic involvement, are the goals of the treatment.

Bibliography:

1. Allan Gibofsky, MD, JD, FACP, FCLM; Epidemiology, Pathophysiology, and Diagnosis of Rheumatoid Arthritis: A Synopsis Am J Manag Care, 2014; 20: S128-S135
2. Eunice J. Kim, MD, Harold R. Collard, MD, FCCP, and Talmadge E. King, Jr, MD, FCCP; Rheumatoid Arthritis-Associated Interstitial Lung Disease, 2009 Nov; 136(5): 1397–1405.
3. https://www.arthritis.org/
4. Wasserman AM (December 2011). "Diagnosis and management of rheumatoid arthritis". American Family Physician. 84 (11): 1245–52. PMID 22150658
5. Manson J., Rahman A., "Systemic lupus erythematosus", PubMed, 2006.
6. Fanouriakis A., Kostopoulou M., Alunno A. "2019 update of EULAR recommendations for the management of sistemic lupus erythematosus", 28.03.2019.
7. Almoundi O., Attar S., "Pulmonary manifestations in systemic lupus erythematosus:Association with disease activity", Respirology, 2015.
8. Quismorio F., Torralba K., "Clinical application of serologic tests, serum protein abnormalities and other clinical tests in SLE", Dubois' Lupus Erythematosus and related Syndromes, 8th edition, Elsevier 2012.
9. www.scleroderma.org

17. SARCOIDOSIS

1. General features/Definition

Sarcoidosis (SZ) as defined by ATS/ERS/WASOG, is a systemic disease of unknown cause, which generally occurs in young or middle-aged individuals. The disease is often clinically manifested with bilateral hilar adenopathies, pulmonary infiltrates, eye and skin lesions, but also with other localizations, in various organs (liver, spleen, heart, etc.). The characteristic lesion in histological terms is the noncaseating epithelioid granuloma.

2. Epidemiology

Sarcoidosis is widespread throughout the world, affecting especially people between the ages of 20-40 years. The disease occurs more frequently in women. In Romania, 40 out of every 100 000 people are affected.

3. Etiology, risk factors and pathogenesis

a. Etiology and risk factors

The cause of this pathology remains unknown, but we can consider the following risk factors:

- *environmental factors:* the season (sarcoidosis being most frequently diagnosed in winter and spring), the geographical area (the rural environment being more prone), the water from the well, the pine pollen, the wood smoke, but also the occupation (farmers, poultry farmers, workers in the vehicle industry)
- *infectious factors:* viruses (Herpes Virus, Retrovirus, Epstein - Barr virus), mycobacteria (M. tuberculosis, M. paratuberculosis), other infectious agents (Mycoplasma, Chlamidia pneumoniae, Corynebacterium)
- *genetic factors:* family sarcoidosis (close relatives of the patient are at higher risk to get the disease), race (in Caucasians it manifests itself differently than in African Americans)

b. Pathogenesis

The changes that occur in sarcoidosis are triggered by the immune response to the initial aggression on the part of an antigen or some antigens. Initial immunological abnormalities in sarcoidosis are characterized by the accumulation of macrophages and T lymphocytes in the areas of active inflammation, which is produced by the presence of the antigen/antigens, this process being performed especially at the lung level.

T lymphocytes and activated macrophages, accumulated in the lungs, secrete a multitude of mediators that further develop the specific features of sarcoidosis. Macrophages that are activated by the presence of an antigen at the lung level, secrete proinflammatory cytokines that are responsible for the formation and persistence of granulomas: IL-1, IL-6, IL-12, IL-23, IL-15, IL-18, IL-22, IL-27, GM-CSF, MIP, MCP-1, RANTES, TNFα and fibroblastic growth factors.

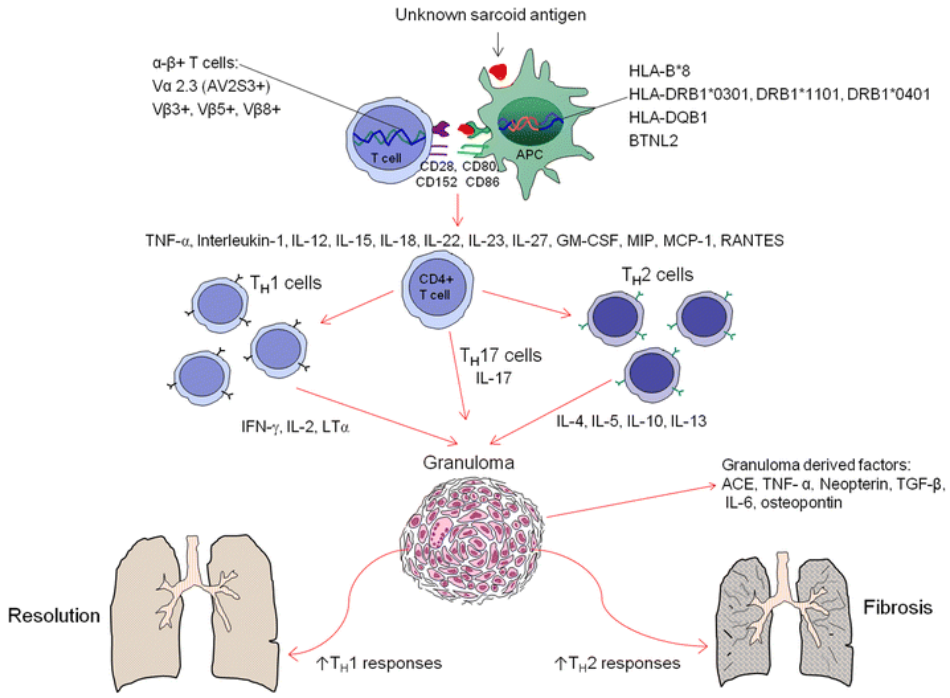


Figure 1. Activated macrophages that release the mediators responsible for pulmonary fibrosis formation (Source: Inflammopharmacology, April 2011, Issue 2, pp55-68)

The immunological peculiarity of sarcoidosis is represented by the accumulation of activated lymphocytes of the helper-inducer type (CD4) in the tissues with active disease. Lymphocytosis with the predominance of *CD4 lymphocytes* in the broncho-alveolar lavage fluid is one of the most important diagnostic markers. Due to the influence of cytokines, macrophages are transformed into epithelioid cells and multinucleated giant cells that will constitute the *noncaseating epithelioid granuloma*, this being the histopathological lesion specific to sarcoidosis. The specific granuloma is capable of persisting, resorbing or evolving into pulmonary fibrosis.

4. Morphopathology

Noncaseating epithelioid granuloma

The characteristic lesion of sarcoidosis is the *sarcoid granuloma*, being an oval granuloma, noncaseating epithelioid consisting of epithelioid cells with radially arranged pale nuclei, the centrally located multinucleated giant cells, being surrounded by lymphocytes, arranged in a reticuline network. The CD4 T lymphocytes are centrally located, and the CD8 at the periphery.

Sarcoid granulomas are most commonly found in the lymph nodes (predominantly intrathoracic), in the lungs, liver, spleen, but also in the skin. In the lungs, 75% of the granulomas are located in the peribronhiolar, perilobular and subpleural connective tissue, following the lymphatics and the pulmonary veins; the most commonly encountered location is in the upper two thirds of the body.

5. Clinic

The clinical expression may be:
• *asymptomatic*: it is usually detected at a random x-ray;
• *non-specific symptoms* (in about 40% of patients): fever, asthenia, fatigue, myalgia, weight loss; to consider the diagnosis of sarcoidosis in fevers prolonged for unknown cause;
• *specific symptoms*: in affecting certain organs.

The symptomatology can be manifested by:

• *acute onset* (in about 18-20% of patients): *Lőfgren's syndrome* - the onset is sudden, with disappearance in 1-2 years; it is characterized by fever (39-40ºC), erythema nodosum, arthritis (predominant at the ankles), uveitis and bilateral hilar adenopathies. In approximately 70% of patients, spontaneous remission occurs in the first two years of onset and do not need treatment, oral corticosteroids are rarely necessary. *Heerfordt syndrome* - fever, facial paresis, hypertrophied parotids, uveitis.
• *insidious onset*: characterized by coughing with or without dyspnea, which tends to become chronic.

Sarcoidosis can occur in any system or organ:

a. *Respiratory system (90-95%):* Patients have dry cough, dyspnea, chest pain. The clinical examination is often normal or with slight changes: sometimes we can detect rales or wheezing, given by lymph node compression. It can also affect the pleura, in rare cases: pneumothorax, pleurisy, chilothorax.

b. *Lymphatic system (75%):* Bilateral and mediastinal hilar adenopathies are encountered. The peripheral lymph nodes that are most commonly affected are the cervical and scalenic ganglia.

c. *Cardiac damage (30%):* The diagnosis of cardiac sarcoidosis is rare, having as a symptomatology rhythm and direction disorders or sudden death that can occur as unique event in sarcoidosis with cardiac location.

d. *Skin damage* (25%): Skin lesions that appear in sarcoidosis can be of several types: erythema nodosum; erythematous plaques, papules; transformation of old scars (keloid scars); lupus pernio: purple induration, with depigmented areas.

e. *Ocular impairment (20-30%):* Acute uveitis most commonly occurs, which is characterized by blurred vision, tears and photophobia. Anterior chronic uveitis (iridocyclitis) can lead to glaucoma or cataract, and posterior uveitis leads to retinal detachment and loss of vision.

f. *Hepatic damage (20-80%):* Most often it is asymptomatic, with only an increase in the size of the liver (hepatomegaly) and hepatic transaminases.

g. *Nervous system damage (<10%):* It is manifested by: encephalopathy, meningitis, cerebellar, spinal cord and hypothalamus damage, and of the peripheral nervous system through peripheral neuropathy or radiculopathy.

h. *Osteo-articular and muscular system (8-40%):* Acute arthritis located in the region of the ankles, knees, elbows, metacarpophalangeal joints and myalgia is manifested at this level.

i. *Urinary tract* (10-30%): We can detect granulomas that lead to glomerulonephritis or granulomatous interstitial nephritis.

j. *Spleen* (30-60%): splenomegaly.

6. Investigations

Sarcoidosis evaluation algorithm – Evaluation modalities/procedures:

1. History (occupational, exposure to environmental factors, symptoms)
2. Clinical examination
3. Antero-posterior thoracic X-ray; ± HRCT; ± bone x-ray (hands)
4. Functional pulmonary tests: Spirometry and DLco
5. Biological tests ACE (angiotensin-convertase), Full Blood Count (Leukocytes, Hematites, Platelets)
6. Biochemistry: serum calcium, liver enzymes, creatinine
7.Urine examination (hypercalciuria)
8. ECG: ± 24-hour Holter monitoring, ± Echocardiography, ± cardio-MRI
9. Retinal ophthalmologic examination
10. Tuberculinic skin test and QuantiFERON-TB Gold
11. Bronchial endoscopy with mucosal and transbronchial biopsy. Mediastinoscopy with biopsy.
12. Histopathological examination
13. Broncho-alveolar lavage with CD4 / CD8 determination

a. Imaging examination: *Chest x-ray*: The presence of bilateral, symmetrical, bulky adenopathies shows that the disease is recent, returning in the first two years from the onset. The most used staging is the one based on the elements offered by the radiological examination (Table 1.)

Table 1. Radiological staging of chest damage (Scadding):

Stage	Aspect	Radiological Frequency	Spontaneous resolution at 5 years
0	Normal chest x-ray	5-10%	-
I	Bilateral hilous adenopathies	50 %	80%
II	Bilateral hilous adenopathies and pulmonary infiltrates	25%	68%
III	Lung infiltrates without bilateral spinal adenopathies	15%	33%
IV	Pulmonary fibrosis	5-10%	0

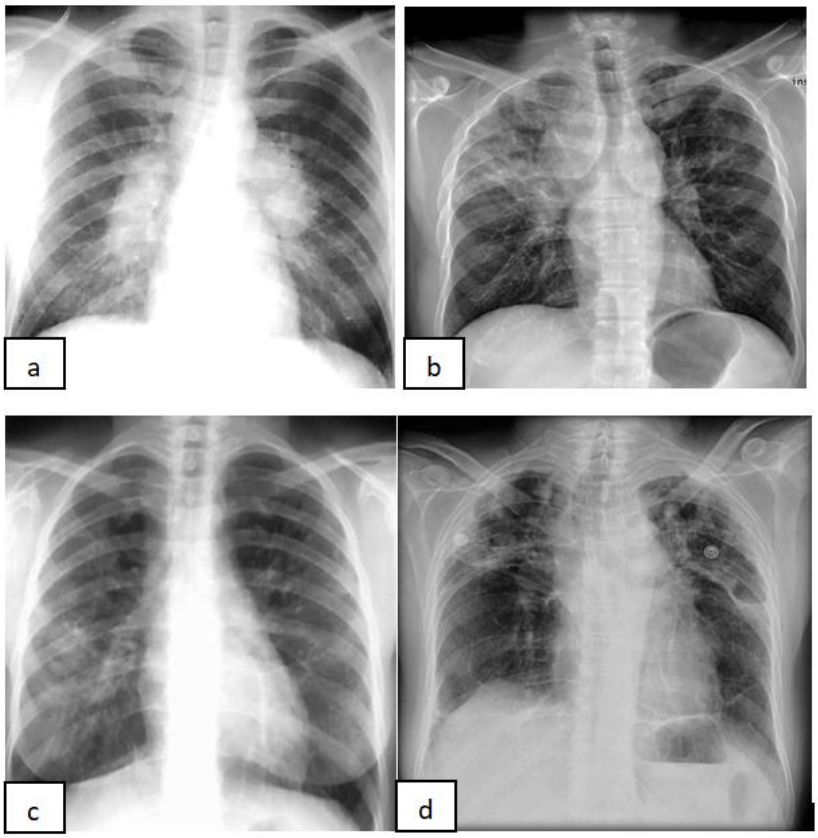


Figure 1. Pulmonary sarcoidosis-Stadialization of radiographic aspects. (a) Stage I -nodular opacities located hilar bilaterally . (b) Stage II-hilar opacities and Upper pulmonary infiltrates. (c) Stage III- infiltrate medio-pulmonary in right lung . (d) Stage IV-Scar reticulation opacities, retractances in the upper bilateral lobs.

Chest CT: It is useful for highlighting the mediastinal localization and extension in the lung parenchyma, lesions that may not be detected on the chest X-ray. Thus, it can detect: hilar/ mediastinal adenopathies, opacities in the aspect of "matte glass", perilymphatic nodules, reticular infiltrates, traction bronchiectases, "honeycomb" appearance, fibrosis.

PET scan (Positron Emission Tomography): is used to detect hidden lesions.

b. Respiratory functional explorations: Spirometry can detect restrictive ventilator dysfunction (70% of cases). It may also be associated with decreased DLco (occurrence of pulmonary fibrosis). Bronchial hyperreactivity occurs in 20-30% of patients.

c. Bronchoscopy: In 15-20% of cases endobronchial changes may be encountered: hyperemia or edema of the bronchial mucosa, capillary dilation, yellowish micro - or macronodules, bronchial and tracheal stenoses, traction. For the histopathological examination, biopsies of bronchial mucosa, nodules or puncture are most frequently performed - *transbronchial lymph node or pulmonary biopsy (VATS).*

d. Mediastinoscopy performed under general anesthesia, by superior incision of the sternum, which allows visualization of the mediastin and biopsies taken from a lymph node or lung tissue.

e. Broncho-alveolar lavage (BAL): BAL profile in sarcoidosis: Lymphocytes increased in over 90% of patients; number of neutrophils can be increased in advanced stages of the disease; in sarcoidosis, lymphocytosis is characteristic and an increased CD4/CD8 ratio (over 3.5%). A ratio greater than 5, which correlates with clinical and radiological data, leads to a diagnosis of sarcoidosis, even without histopathological confirmation. Neutrophils grow in BAL when pulmonary fibrosis occurs.

f. Serum angiotensin-convertase (SAC): Being secreted at the level of granulomas, it will have high serum values (the normal value being between 15-28 u/ml) and it will guide us on the expansion and activity of the granulomatous mass. It is not specific in sarcoidosis, it can grow in other pathologies as well (tuberculosis, silicosis, hyperthyroidism)

7. Diagnostic strategy/Positive diagnosis

In order to diagnose the disease as accurately as possible, several steps must be followed:
Clinical and imaging examination;

b. Presence of noncaseating epithelioid granuloma (morphopathological examination);

c. Exclusion of other pathologies that could cause the same clinical, imaging and histological changes.

8. Differential diagnosis

Often, sarcoidosis can be a difficult to diagnose pathology. Below are listed the diseases in which the granulomas are present at the histopathological examination:

1. Infections: *Bacteria* Brucella, Borrelia, Yersinia; *Mycobacteria* M. tuberculosis, M. leprae; *Spirochete* Treponema palidum; *Fungi*: Aspergillius; Protozoa Toxoplasma, Leishmania; *Metazoaires* Toxocara, Schistosoma; *Viruses* Epstein-Barr, Herpes, Rujeolic, Rubeolic, Cytomegalovirus;
2. Extrinsic allergic alveolitis: Farmer's lung;
3. Neoplasms: mediastinal lymphoma, Non-Hodgkin lymphoma, NSCLC, small cell lung cancer;
4. Chemicals: Beryllium, aluminum, zirconium, silicon, talc, silicone, titanium;
5. Idiopathics: Sarcoidosis, Crohn's disease, primitive biliary cirrhosis, granulomatous hepatitis, Wegener's granulomatosis, systemic lupus erythematosus
6. Pulmonary Tuberculosis
7. Hypersensitivity Pneumonitis

9. Management/ Treatment

Because in a large number (60-70%) of patients sarcoidosis is remitted spontaneously, immediate initiation of drug therapy is not recommended. Such situations can be encountered at:

• asymptomatic patients with radiographic stage 1 (bilateral spinal adenopathies);
• patients with radiographic stage 2 and with moderately modified lung function, which does not progress in 6-12 months;
• patients with radiographic stage 3 and with moderately modified pulmonary function, which does not progress at 6 months.

Treatment will be instituted in patients with severe, progressive pathology and in those associated with extrapulmonary sarcoidosis. Because the cause of the disease is not yet accurately known, there is no etiological treatment.

Corticosteroid medications are considered the first line of treatment for sarcoidosis that requires therapy. Oral corticosteroids effectively reduce systemic inflammation in most people, thereby slowing, stopping or even preventing organ damage. Corticosteroids may be prescribed alone or combined with immunosuppressant agents like methotrexate and azathioprine or the antimalarial drug (hydroxychloroquine) introduced into refractory disease. Topical corticosteroids may be prescribed for cutaneous involvement, and eye drops may be prescribed for uveitis. Corticosteroid inhalers may be useful in those with evidence of bronchial hyperactivity.

There are several treatment schemes for oral corticosteroids in sarcoidosis, of which we recommend the following: the initial (attack) dose is 0.5-1 mg/kgc/day, for 4-6 weeks, followed by a reassessment where we identify improving or stopping the disease by gradually lowering the dose by 5-10 mg every 4-8 weeks until 15-30 mg/day; if the favorable evolution continues, a maintenance dose of 10-15 mg/day, continued for 12 months, will remain.

Other drug treatments are: immunosuppressive agents (methotrexate, azathioprine, leflunomide, cyclosporine, cyclophosphamide, chlorambucil, hydroxychloroquinine), and as alternative options: immunomodulatory agents (Pentoxifylline, Thalidomide, Infliximab - anti-TNFα), pulmonary transplant (in extended and mutilating fibrosis).

10. Evolution and prognosis

The positive prognostic factors would be: radiological stage 0 and 1 and Löfgren's Syndrome.

Negative prognostic factors: onset after 40 years, symptomatology that persists for more than 6 months, damage of more than 3 organs, certain extrapulmonary locations (heart, nervous system, spleen, osteo-articular, ocular), radiological stage 3 and 4, decreased pulmonary volumes or alveolo-capillary diffusion below 60%, the presence of pulmonary arterial hypertension.

The evolution and prognosis of sarcoidosis depend on the clinical manifestations, the biological analyzes and the imaging extension, which must be performed periodically.

The natural evolution of sarcoidosis

- Spontaneous remission: 60-70%
- Progressive evolution towards chronic disease:10-30%
- Permanent sequelae:10-20%
- Mortality: 1-5% (respiratory, central nervous system, cardiac)

Bibliography

1. ATS / ERS Statement on Pulmonary rehabilitation. Am J Respir Crit Care Med 2006, 1390-1413
2. Sarcoidoza - Diana Ioniță, Casandra Cîlț, Ruxandra Ulmeanu - Editing Prof. Dr. Ioan Stoicescu, Curtea Veche publishing house, Bucharest, 2012
3. Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, Eklund A, Kitaichi M, Lynch J, Rizat G, Rose C, Selroos O, Semenzato G, Sharma OP. ATS / ERS / WASOG statement on sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 1999 Sep: 16 (2): 149-73
4. Pneumology course for resident doctors - Under the editorship of Prof. Dr. Voicu Tudorache, Mirton Timișoara Publishing House, 2013, Pag. 215-224
5. Sarcoidosis - Donald N Mitchell, David R Moller, Stephen G Spiro, Athol Wells, CRC Press of Taylor and Francis Group, 2012
6. Atlas of Sarcoidosis Pathogenesis, Diagnosis and Clinical Feautures - Violeta Mihailovic-Vucinic MD PhD, Om P. Sharma, MD, MRCP (Lond.), FACP, FCCP, D.T.M. & H (Eng.), Springer – Verlag London Limited, 2005
7. Textbook of Respiratory Medicine 5th Edition - Robert J. Mason MD, V. Courtney Broaddus MD, Thomas R. Martin, MD, Talmadge E. King, Jr., MD, Dean E. Schraufnagel, MD, John F. Murray, MD, FRCP, DSc, Jay A. Nadel, MD, DSc (Hon), DLaw (Hon), Pages 1427-1445
8. Inflammopharmacology, April 2011, Issue 2, pp55-68

18. TUBERCULOSIS

Definition

Tuberculosis (TB) is a specific infectious - contagious disease, endemic, produced by bacteria of the genus Mycobacterium (main agent Mycobacterium tuberculosis), with predominantly pulmonary localization but also in other organs, with chronic consumptive evolution. It is often fatal and widespread in the population.

Etiology

The etiological agent of tuberculosis in humans is *Mycobacterium tuberculosis (MTB)* or the Koch bacillus which is part of the Mycobacterium genus.

The genus Mycobacterium includes several species: *Mandatory pathogenic mycobacteria* (M. leprae and M. tuberculosis- M.tuberculosis, M.bovis, M.africanum) and potentially pathogenic (*slow-growing*: M. Kansassii, M. Marinum, M. Simiae, M. scrofulaceum, M. Xenopi, M. Szulgai, M.avium, M. intracelularae, M.ulcerans and *fast-growing* M.fortuitum, M.chelonei) which has a similar clinical disease but of unequal epidemiological importance.

MTB is an acid-fast bacilli slightly curved of 0.2 - 0.5 microns in diameter; 2 - 4 microns in length, which grows slowly with a multiplication time of around 18-24 hours, thus requiring at least 3 weeks for the appearance of visible colonies on the solid culture media and 1-2 weeks for the liquid culture media.

MTB is an obligate aerobe, oxygen-rich tissues being the most likely to be invaded. It is a facultative intracellular parasite; its virulence being largely related to the ability to survive and multiply in the intracellular environment of mononuclear phagocytes. The bacilli are rapidly destroyed in the environment by ultraviolet radiation (sunlight).

Transmission and pathogenesis

The transmission and pathogenesis of tuberculosis are inseparable, MTB is dependent on its human host to survive.

The sources of infection are the persons with TB disease (> 95%), the animals with TB disease and the environment contaminated by the patients (dust in the house, food and objects)

The main transmission factor of the tuberculosis infection (*the reservoir for MTB*) is the *patient with* a form of tuberculosis that communicates with the external environment is the main, the greatest epidemiological danger being the pulmonary localization, which is also the most common form of TB (90%).

The ways of TB transmission (through which the MTB enter the human body) are represented by:

- *the airway* (coughing, singing, sneezing, talking) is the most frequently leading to the infection grafting in a new host (92%); the contamination being made through the infectious droplet nuclei, the "Flugge drops", which the patient generates through speaking or coughing (a 2 cm cavern contains 100 million bacilli!);
- *the digestive tract* is of less importance (5%), the contamination being made by ingesting bacilli from contaminated food (milk or non-sterilized milk products) or by mouth contact with the infected hands or objects (small children);

- *intrapartum infection* transmission is possible by aspiration of amniotic fluid containing MTB, as well as by the interruption of the placental barrier during labor, when the bacilli can enter the fetal circulation and cause a granulation;
- *the genital tract* transmission appears when the male partner suffers from advanced untreated epididymal tuberculosis;
- *skin or mucosal infections* (skin, pharynx, conjunctiva) are exceptional.

MTB access in the body exposed to contamination varies according to the characteristics of the sources of contagion: density, permanent or intermittent character of the emission of bacilli in the environment.

The MTB interaction with the human host begins when the infectious droplet nuclei containing microorganisms from the contagious patient are inhaled. An optimal interaction between the host and the pathogen results in the transmission of the infection. Primary infection is usually limited and followed by a variable latency period.

Any MTB multiplication site (including after dissemination) may constitute a future localization of tuberculosis, either in the continuation of the initial multiplication (by progression of exogenous infection or reinfection), or remotely in time, after stopping the initial multiplication (endogenous reactivation).

Tuberculosis epidemiology

Definitions:
Latent tuberculosis infection (LTBI) defined by positive tuberculin response, without clinical, radiological and bacteriological manifestations.
Active tuberculosis - disease (TB) characterized by the presence of clinical and/or radiological manifestations caused by the multiplication of MTB in the human organism and its response.
The case of tuberculosis is the patient with TB bacteriological or histopathological confirmed diagnostic or the patient who has no confirmation, but with a full course of anti-TB therapy prescribed by a clinician

The natural history of the disease

When discussing the natural history of TB disease, we must consider the existence of the source and three events:

- *transmission of tuberculosis* which is exclusively human except in rare cases of transmission between species (especially from bovines); transmission occurs when the bacilli begin to multiply in the new host that made the primo infection, but the moment of transmission cannot be specified;
- *the transformation of the infection into the disease* depends on the ratio between the multiplication and dissemination of MTB and the host defense mechanisms; thus, at more than 90% of the immunocompetent persons the host defense mechanisms prevail over the microbial population;
- *perpetuation of the disease* (endemic character) by closing the disease transmission cycle.

The interaction between the healthy organism and the MTB remains with no results in 70% and only in 30% of cases results in infection of the organism. The infection remains latent in more than 90% of cases. Less than 10% turn into early or late illness. Two separate clinical

entities are thus established which differentiate therapeutic attitude and monitoring of tuberculosis: Latent tuberculosis infection and tuberculosis.

The natural history of tuberculosis can be modified by several factors. In the absence of an immunodeficiency, the risk of developing tuberculosis is estimated at 5-10% of the cases in the first 3-5 years following infection, and 5% for the rest of life. Some situations can facilitate the rapid disease transition: extreme ages (young children under 4 years or older) or associated comorbidities (table no. 1). HIV infection plays a key role in changing the natural history of the disease by increasing the risk of the disease occurring by between 5 and 8% in the first year and 50% for the rest of life..

Table no. 1: Risk of disease in TB infections

Risk factor	Relative risk
recent TB infection (< 1 year)	20 – 80
recent TB infection 1-7 years	2
HIV infection	35 – 140
injecting drug users + HIV infection	40 – 100
injecting drug users without HIV	10
silicosis	30 – 70
radiological abnormalities-TB sequels	2 – 4
kidney failure	4 – 9
diabetes mellitus	4 - 6
underweight	2 – 3
absence of the above factors	1

Epidemiometric indicators in tuberculosis

Tuberculosis (TB) because of its endemic character is the most widespread and persistent infectious disease in humans. About one third of the world's population is infected with MTB. The World Health Organization (WHO) estimates 10 million new cases of active tuberculosis each year and about 1,5 million deaths through tuberculosis.

The study of the epidemiology of tuberculosis (TB) allows to measure the extent of the disease and its evolution over time, spontaneously or as a result of the application of the disease control measures.

In 2017, in Europe, an incidence of over 30 cases per 100 000 population was registered in several countries such as: Republic of Moldova (82,9), Romania (62,7), Ukraine (61,6), Russia (58,7). It is obvious that most developed countries have low indicators, which suggests that the socio-economic standard influences the health status of the population.

However, it is worth mentioning that the overall incidence of TB in Romania has steadily decreased in the last 18 years, from 142,2 to 100,000 inhabitants in 2002 (when the highest value in the last 30 years was recorded), to 59,4 per 100,000 inhabitants in 2018 (figure no.1).

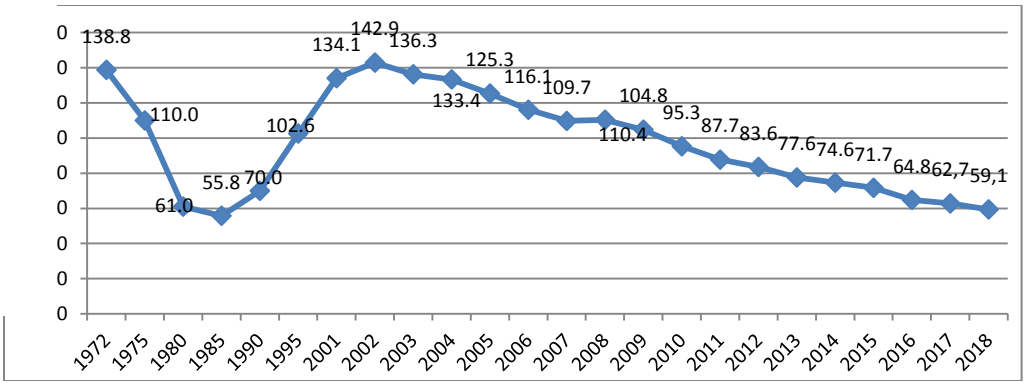


Figure no 1. The global incidence of TB in Romania, from 1972-2018

Before the introduction of anti-tuberculosis drugs and extensive disease control programs, about 50% of tuberculosis patients died. WHO estimates 1.6 million through death TB in 2018, representing the 10th leading cause of death globally due to a single infectious agent.

In Romania, the TB mortality curve followed a steady downward trend, reaching 4.1 per 100.000 population in 2017.

Drug-resistant TB is a major epidemiological problem worldwide, in 2017 worldwide there were 550,000 cases of rifampicin-resistant TB (82% MDR TB of which 8.5% XDR TB); the number of MDR cases representing a faithful indicator of both the quality of the treatments administered and the efficiency of the control measures for the transmission of the infection.

In Romania, in 2018 there were 396 cases with MDR TB, of which 43 with XDR TB.

Methods in TB diagnostic

Clinical signs and symptoms of tuberculosis are non-specific and, in some cases, the active disease may be asymptomatic so that the diagnosis cannot be made on the basis of clinical data alone.

The methods used in the diagnosis of tuberculosis can be grouped into classical (conventional) methods and modern methods of diagnosis.

The classical (conventional) methods used by routine in the diagnosis of tuberculosis are radiological examination, tuberculin skin testing (TST), bacteriological investigation (microscopy, cultivation of mycobacteria in solid medium and sensitivity testing) and histopathological examination.

Modern diagnostic methods, faster and more sensitive than the classical methods, are: automatic methods of cultivating mycobacteria in the liquid medium, sensitivity tests, molecular biology and genotyping techniques, interferon gama relase assay; methods that are used in our country.

1. Classic methods of diagnosis

A) Radiological examination

Standard chest x-ray (two incidences: postero - anterior and profile) is an essential component in the diagnosis of pulmonary TB, and often the first paraclinical investigation to be used, this being justified by the fact that, in practice, a normal thoracic image almost always excludes pulmonary tuberculosis. General radiographic elements *that may suggest* pulmonary

tuberculosis are: localization of the image at the apex of the lung in the apico-dorsal or apical segments of the lower lobe, polymorphic aspect of the images: cavities, infiltrative, nodular, coexisting with calcifications and pleural sequel, asymmetry of bilateral images, very fine miliary images, slow image dynamics.

Chest CT scan is a radiographic method that allows the exact location of the site and the extent of pathological images, visible on the x-ray and additionally it can specify the existence of lesions (caverns, dilated bronchi, tumors) of the hilum and mediastinum, which do not appear on a regular x-ray.

To be noted, the radiological diagnosis (standard x-ray or tomography) of active pulmonary tuberculosis is uncertain, but only for guidance, as a rule the diagnosis must be confirmed by the bacteriological examination (conventional and / or molecular and genetic).

B) Tuberculin skin test

The tuberculin skin test (TST) is used as a screening tool (for diagnostic and epidemiological purposes) for the detection of MTB infection.

TST is quantitative and consists of the intradermal injection (by Mantoux technique) of MTB-tuberculin antigen (*protein purified derivative*, PPD), which produces at the injection site, an inflammatory reaction if the body is infected with MTB. The substrate is constituted by the sensitized and circulating T lymphocytes in the blood, whose activation in cascade produces delayed-type hypersensitization, expressed macroscopically through a zone of induration at the injection site.

Tuberculin preparations are standardized internationally, currently there are two preparations: PPD-S (0.1ml contains 5UI PPD) and PPD-RT-23 (0.1ml contains 2UI bioequivalent to 5UI PPD-S); in Romania, the 5UI preparation is used.

Testing technique

The TST should be performed, read and interpreted by *experienced personnel*, to ensure a more rigorous administration and a correct reading.

Materials required to perform TST (Mantoux technique): 1 ml single-use watertight syringe, divided into 0.10 ml, with special needle for intradermal injections (10 mm, with short bevel), tuberculin – PPD 5IU/0, 1ml (check the validity and quality of the product), antiseptic solution – 75% alcohol, medicinal wool.

Place of inoculation: preferably the anterior face of the left forearm, at the limit between 1/3 upper and middle, in healthy skin.

The technique of administration must be very rigorous according to the following steps:

- disinfection of the skin with antiseptic solution,
- stretching the skin by folding the teguments on the dorsal face of the forearm to facilitate the strictly intradermal introduction of tuberculin,
- 0.1 ml PPD (5UI PPD) is intradermally injected, which usually produces a 5-6 mm ischemic papule with an "orange peel" appearance; this should not be buffered after the needle has been removed,
- the correct test is confirmed by the *lack of bleeding and by obtaining the papule*.

Reading the test is quantitative and is made between 48 and 72 hours (ideally at 72 hours to avoid underestimation of the result) from the administration of tuberculin, when the induration is maximum and the non-specific reaction disappears, and consists of:

- check the injection site under good light;

- *the transverse diameter* of the indentation zone is measured using a transparent ruler, the limits are marked, after the extreme points of the transverse diameter have been palpated and delimited; *the longitudinal diameter and the erythema are not measured;*
- the result is recorded in millimeters (the result is not recorded as "positive" or "negative", if you do not find any induration, the recording will be 0 mm),
- note the date of the reading.

Interpretation of the skin test depends on the measurement in millimeters of the induration, the risk of the person tested to be infected with MTB and the progression of the disease (if infected):

✓ **depending on the diameter of the induration:**

- ***tuberculin reaction ≥ 10 mm*** is considered positive in immunocompetent persons; can mean not only MTB infection, but also M. bovis vaccination or natural,
- ***tuberculin reaction ≥ 5 mm*** is considered to be at risk for progression to disease for immunosuppression situations (in HIV infected, other immunosuppression situations, patients with organ transplants, immunosuppressive treatment, anti-TNF alpha treatment);
- ***tuberculin reaction ≤ 9 mm*** signifies post-vaccine BCG allergy in the first years after birth or infection with non-tuberculous mycobacteria (exception: HIV infected/ or other immunosuppression situationss and anti-TNF alpha treatment)
- ***moderate reaction, 10-14 mm***, suggests natural MTB infection;
- ***the intense reaction, over 15 mm (hyper-ergy)***, signifies the infection with MTB, not necessarily active tuberculosis, probably increased risk of lesion evolution.

✓ **depending on consecutive tests (at 6-8 weeks interval):**

- ***the tuberculin turn*** represents the transition from a negative to a positive reaction if it is not the consequence of a BCG vaccination, translating latent tuberculosis infection recently;
- ***tuberculin jump*** represents the increase of the diameter of the tuberculin reaction by more than 10 mm compared to the previous test; the significance is uncertain;
- ***the conversion*** represents the increase of the reaction by more than 10 mm at a retest, within 2 years; it is estimated that the phenomenon signifies the progression of tuberculosis infection to TB disease; TST conversion occurs at 6-8 weeks after infection (infectious contact).

The limits of interpretation

False-positive reactions: BCG vaccination, technique/interpretation incorrect of TST, allergic child to proteins, infections with atypical mycobacteria, booster effect, tuberculin inactivated by storage.

False-negative reactions: severe forms of tuberculosis in infants and young children, HIV infection, viral infections (varicella, measles), immunosuppressive medication (corticosteroids, anti-TNF alpha), lymph nodes (Hodgkin / non-Hodgkin's lymphoma, leukemia, sarcoidosis) , primary immunodeficiency, recent vaccinations with live viruses, malnutrition/ hypoproteinemia, shock, inactivated tuberculin through improper storage and use, incorrect technique/reading, initial stage of tuberculosis infection (before the immune response - *"anergic window"*).

Positive reaction to tuberculin is a marker of tuberculosis infection, without correlation with active tuberculosis. The negative TST does not exclude the diagnosis of tuberculosis.

Contraindications: TST mainly has no contraindications. It is recommended to postpone in the following situations: fever / acute illness, eruptive diseases, corticosteroid treatment.

***Incidents/accidents most frequently encountered*:** marked edema and inflammation, produced by the subcutaneous introduction of tuberculin (administration error).

C) Conventional bacteriological examination

Clinical samples (pathological products). Depending on the location of the disease, the pathological products subjected to examination for MTB evidence are:

- ***Pulmonary TB:*** sputum or induced sputum (aerosols, lavage, bronchial aspirate, gastric lavage) collected in standardized containers with transparent walls, volume of 30-50 ml, with a diameter of 3-4 cm, with a screw-in lid. The sputum collection must be carried out in specially arranged spaces - "sputum collection rooms" with storage stored in the refrigerator (+ 4 ° C) and transported to the laboratory as quickly as possible.
- ***Extrapulmonary TB:*** serous fluids (pleura, pericardium, peritoneum), cerebrospinal fluid, urine, punctate lymph node or joint, bioptic fragments. Collection is carried out under strict conditions to avoid contamination of the products, and to allow the cultures to be carried out without prior decontamination. Biotic fragments are not fixed by means of formalin or other fasteners if they are intended to make decultures for MTB.

The microscopic examination is performed on the pathological product and identifies the mycobacteria that have properties of acid-alcohol resistance (BAAR).

The microscopic examination is performed on the smear of the pathological product and identifies the mycobacteria that have properties of fast acid bacilli (AFB). The colors used to identify the fast acid bacilli are:

- *Ziehl-Nielsen staining* is the reference standard for the identification of mycobacteria from biological and pathological products (sputum emitted spontaneously and induced; bronchial aspirate and laryngeal-tracheal secretions; gastric aspirate; CSF; urine; pleural fluid, pericardial, peritoneal, synovial; lung, bronchial, lymph node biopsy samples, etc.). The examination is performed under the optical microscope with 100x immersion objective, mycobacteria appearing as thin sticks, red, slightly curved, more or less granular rods, isolated or grouped in pairs or groups, on a blue background (figure no.2a). The results are expressed semi-quantitatively depending on the density of the bacilli on the blade (table no. 2). The sensitivity of the examination is relatively low (it identifies the pathogen only in the pathological products rich in bacilli over 5.000-10.000 germs/ml) and does not provide information on the viability of the bacilli, identity, sensitivity to drugs.

- *Staining with fluorochromes (auramine, rhodamine)* uses the fluorescence microscope (figure no.2b). It is a fast method, shorter examination time, with 10% higher sensitivity than conventional staining and has the role of eliminating negative smears by reducing the number of conventional colored blades. The positive result requires confirmation by Ziehl-Nielsen staining.

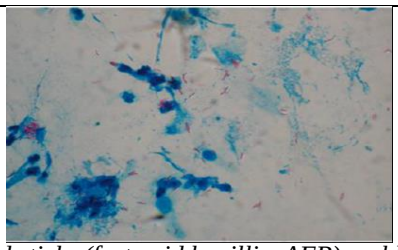
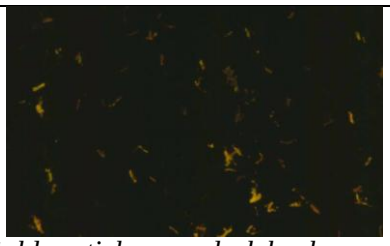
 *Red sticks (fast acid bacilli =AFB) on blue background*	 *Golden sticks on a dark background*
Figure no.2a. Sputum smear Ziehl-Nielsen staining, 100x.	***Figure no.2b: Staining with fluorochromes (auramine, rhodamine)***

Table no. 2. Semi-quantitative expression of microscopic examination in Ziehl-Nielsen staining

Numbr of AFB identified (seen)	Microscopic fields examined	Result
Absent	≥ 100	Negative
1-9 AFB/100 fields	100	Notify no. exactly from AFB/100 fields
10-90 AFB/100 fields	100	AFB positive (+)
1-10 BAAR/ field	≥ 50	AFB positive (++)
≥10 BAAR/ field	≥ 20	AFB positive (+++)

Examination by culture on solid medium. Löwenstein-Jensen solid culture is the "***gold standard"*** for the diagnosis of tuberculosis confirmation, with a sensitivity of 80-85% and a specificity of up to 98%. It is performed for all pathological products even if the smear is negative.

The culture test has a much higher sensitivity than microscopy, detecting MTB even if the number of germs in the product examined is low (only 10 germs / ml).

In addition, examination by culture allows the identification of the mycobacterial strain and subsequently its sensitivity to anti-tuberculosis drugs. The period needed to identify the growth of mycobacteria in this medium is 6-8 weeks, due to the slow multiplication of MTB.

The MTB colonies on solid medium are round, pale yellow, conopidiform, with a rough surface (figure no. 3a), isolated or confluent depending on the density of the bacilli in the initial inoculum (figure no. 3b). The expression of the results by culture is made semi-quantitatively depending on the density of the colonies on the culture tube (table no.3).

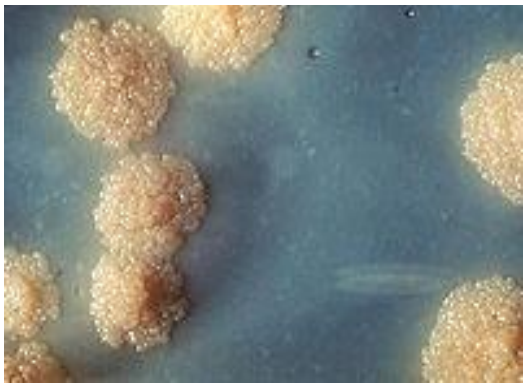


Figure no. 3a. MTB colonies

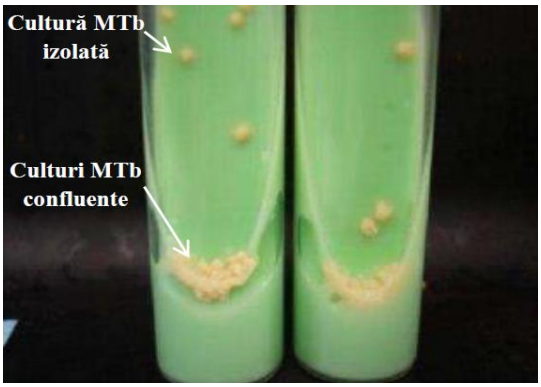


Figure no. 3b. MTB cultures

Table no. 3. The semi-quantitative expression of the examination by culture on the Löwenstein-Jensen medium

Macroscopic suggestive character for MTb	Notation of results
Absence of colonies in the 9 tubes	Negative culture
<30 colonies	No. of colonies / culture tube
30-100 colonies	Positive culture (+)
>100 isolated colonies	Positive culture (++)
Confluent colonies	Positive culture (+++)
Superinfection on 2 or 3 culture tubes	Superinfected culture

Sensitivity tests (antibiograms) in the solid medium for MTB provide information regarding the sensitivity / resistance of the isolated strain to anti-tuberculosis drugs.

In Romania, it is recommended to perform sensitivity tests on all the positive cultures identified during the TB diagnosis (new case or retreatment) and during the monitoring of the treatment if the culture remains positive or reconverse after 4 months of treatment.

The sensitivity tests currently performed in our country are those for Isoniazid and Rifampicin, in order to identify patients with MDR TB; The extended sensitivity tests (and other anti-tuberculosis tests) are performed only in the national reference laboratories (NRL) or the regional reference laboratories (RRL) specially designed / equipped for this purpose.

Cultures and sensitivity tests for anti-tuberculosis drugs are performed only by laboratories with expertise and experience in this domain and which are part of a quality control system for bacteriological diagnosis.

D) Histopathological examination

Histopathological examination is a useful method especially in the diagnosis of extrapulmonary tuberculosis. The clinical samples collected, for the histopathological examination, depend on the location of the disease; the most commonly used and harvesting methods are:

- pleura (blind spot-biopsy on needle, less thoracoscopy),
- lymph node (surgical biopsy),
- bone / synovial membrane (surgical treatment),
- pericardium or peritoneum (surgical biopsy),
- rare bronchial, laryngeal wall (endoscopic biopsy),
- rare lung (surgical biopsy),
- very rarely other locations.

Histological lesions found in tuberculosis can be an adjunctive means for positive diagnosis, when the bacteriological examination is inconclusive.

Isolation of MTB from a clinical sample is the ideal diagnostic method; therefore, *any clinical sample, including tissue fragments, should be cultured for MTB isolation; this requirement taking precedence over the histopathological examination.*

The presence of the gigantic epithelioid granuloma necrosis is relatively specific for tuberculosis, but it is less specific than the culture for MTB.

However, the presence of giant-epithelioid granulomas without necrosis is even less specific, as they may occur in other granulomatous diseases: sarcoidosis, berylliosis, leprosy, syphilis, endemic mycoses, collagen diseases, some vasculitis, etc.

2. Modern methods of diagnosis

A) Fast culture methods in the liquid medium that allow radiometric and colorimetric detection of mycobacterial growth after 1-2 weeks**.** The fast culture methods currently available in Romania are the BACTEC MGIT system and VersaTREK, but these methods are more expensive and less available.

B) The sensitivity tests (antibiograms) for MTB in the liquid medium currently available in Romania are: in the MGIT 960 system, the sensitivity testing of line I and line II antibiotics (less Cs) for isolated mycobacterial strains can be performed automatically.

C) Molecular biological and genotyping methods available in TB bacteriology laboratories in our country are represented by:

- **Nuclear amplification tests (MPT64 Antigen)** quickly identify (within 15 minutes) the MTB complex; mandatory test to confirm the membership of mycobacteria cultures in the MTB complex, both for positive cultures in solid and liquid medium.
- **GeneXpert Ultra (Xpert MTB / RIF)** molecular screening method, a complex MTB and rifampicin resistance, uses PCR technique (polymerase chain reaction) using a sputum sample and other pathological products (gastric/bronchial aspiration, puncture fluids, tissue fragments). The test is very fast and lasts about two hours, the specificity and sensitivity of the method being high: 92.2% -98.2% respective to 99.2%.

D) Interferon gamma releasing assay

Interferon gamma releasing assay (IGRA) is a new test for rapid *in vitro* immunological diagnosis of MTB infection. They are indirect tests (detect cell-mediated immunity as well as TST) and are intended for the diagnosis of latent tuberculosis infection and for the diagnosis of tuberculosis of the child in association with risk assessment, radiological examination and other and other medical assessments.

IGRA assays use specific MTB proteins encoded by genes located at the MTB genome level. These antigens are not found in Calmette Guerin bacilli (BCG vaccine) or in non-tuberculous mycobacteria species so they can differentiate MTB infection from BCG postvaccine allergy.

Like TST, IGRA tests cannot differentiate latent tuberculosis infection from tuberculosis disease and do not confirm active tuberculosis.

Currently, two IGRA tests are available globally: QuantiFERON-TB (QFT) and T-Spot.TB (T-Spot); only the QFT test is available in Romania.

QuantiFERON-TB (QFT) is a gamma interferon dosage assay that stimulates whole heparinized blood cells. Detection of γ-interferon (IFN-γ) produced by stimulated lymphocytes is performed by the Enzyme-Linked Immunosorbent Assay (ELISA). The collected blood (venous blood) is incubated with M. tuberculosis antigens (16-24 hours), then centrifuged, and the INF γ produced is measured by the ELISA reaction, the machine automatically generating the result. The positive test result is 0.35UI IFN-γ / ml.

Latent tuberculosis infection

Latent tuberculous infection (LTBI) is characterized by the presence of MTB in the body, without signs and symptoms, or radiological or bacteriological parameters of active tuberculosis.

Currently about one third of the world's population is infected with MTB. Without treatment, approximately 5-10% of people with LTBI will go into active disease stage at some point in their life; the risk increases under conditions of decreased immunity, in HIV infected persons the risk of progression of LTBI to TB disease is 7-13% annually.

The recommendations of the WHO EndTB Strategy to touch the goal of TB elimination are to identify and treat people with ITBL at risk for active disease progression. TB prevention has major implications for public health, this is why it is essential to identify and treat everyone with risk factors for tuberculosis.

Diagnosis of latent tuberculosis infection

The tests for the diagnosis of LTBI are the tuberculin skin test and the interferon gamma releasing assay.

LTBI does not benefit from a "gold standard" for diagnosis, so it is recommended to use an *LTBI screening algorithm*, based on TST as usual test (depending on the financial possibilities IGRA tests can be used), information collected from medical history, clinical signs, chest x-ray and in some circumstances sputum examination:

- *medical history* helps to obtain information on positive outcomes of TST or IGRA, treatments for LTBI or TB disease;

- *chest x-ray* helps to differentiate between LTBI and active TB in people with positive tests for tuberculosis infection. It is recommended in the following situations: positive tests for LTBI, close contact of a TB patient in case of negative tests for LTBI, in children under 5 years and in people with sequelae lesions.
- *bacteriological examination of sputum (microscopy and culture)* - is recommended in people with positive test results for LTBI and chest x-ray with changes or in situations of respiratory symptoms with normal radiography.

Treatment of latent tuberculosis infection

Prophylactic treatment with Isoniazid (PTI) is an important intervention to prevent and reduce the risk of active TB, there is no evidence that PTI increases the risk of developing isoniazid resistance.

- **PTI indications:**
  - ✓ *Children over 12 months of age* who are unlikely to have active TB based on symptom screening and who have contact with TB case:
    Isoniazid (H), 10 mg/kgc/day, given daily for 6 months (10 mg/Kgc/day, maximum 300 mg/day).
  - ✓ *Adolescents and adults with immunosuppression* (HIV, anti-TNF alpha therapy) who have positive TST and are not likely to have active TB:
    Isoniazid (H), 5 mg/Kgc/ day, given daily for 6 months (maximum 300 mg/day).
- **PTI contraindications** include:
  - ✓ child over 12 months with active hepatitis (acute or chronic) and symptoms of peripheral neuropathy;
  - ✓ adolescent and adult with regular alcohol consumption, active (acute or chronic) hepatitis and symptoms of peripheral neuropathy.

LTBI treatment among contacts of patients with drug- resistant TB. Unfortunately, there are currently very few comparative studies on the use of second-line TB drugs to prevent the disease in the case contact with drug-resistant TB, a reason why WHO does not recommend prophylactic treatment but strict clinical observations and sustained monitoring (at least 6 months from at least two years after the last exposure).

I. TUBERCULOSIS OF THE CHILD

Tuberculosis of the child is difficult to diagnose, even for the pulmonary localization, due to the fact that obtaining the pathological products is difficult (children rarely expectorate) and the pathological products are usually paucibacillary, so that the bacteriological diagnosis most often does not provide the etiological evidence of the disease. In these circumstances, the positive diagnosis of tuberculosis of the child is made through a systemic approach with the corroboration of several elements.

Diagnosis of tuberculosis in children

In current practice, the problem of diagnosing tuberculosis of the child arises in two circumstances: contact with a case of tuberculosis or a child with dragging respiratory symptoms, raising the suspicion of tuberculous etiology. Elements necessary to establish the diagnosis of tuberculosis of the child are represented by:

- ***Epidemiological context*** (known contact with a positive bacteriological TB case)
- ***Suggestive clinical manifestations*** (cough, fever, subfebrility, weight loss over 10%, flictenular keratoconjunctivitis, nodeum erythema, peripheral adenopathy); in the small child- signs of ganglion-bronchial compression: difficulty breathing, hepatosplenomegaly, convulsions, paresis or other meningoencephaltic signs suggestive of miliary dissemination)
- ***TST*** (over 10 mm in those vaccinated with BCG or over 5 mm in those with immunosuppression, turn or tuberculin jump) ± QFT
- Radiological examination (suggestive radiological aspect/CT scan: hilarious or mediastinal adenopathy, pneumonic or bronchopneumonic condensations with hyper transparency included with / without pleural reactions or atelectasis)
- ***Bacteriological examination***: *conventional* (positive in the morning gastric aspirate or bronchial aspirate, sputum induced or spontaneously emitted) and *molecular* (GeneXpert Ultra)
- ***Other investigations*** to support the diagnosis of pulmonary or extrapulmonary TB: bronchoscopy examination (for bacteriological examination, highlighting: fistulas, compression or bronchial stenosis, tissue of peripheral granulation); histopathological examination (suggestive: lymph node, pleural, pericardial biopsy); cytochemical examination (pleural fluid, spinal fluid, pericardial fluid)
- ***HIV test*** in any child confirmed or suspected of TB.

Forms of tuberculosis in children

Tuberculosis of the child can take several clinical forms: tuberculous primo-infection manifest benignly uncomplicated, with benign complications or severe complications.

A) Manifest TB primoinfection benignly uncomplicated - is the consequence of infection of the body with MTB, previously free of TB, followed by suggestive clinical, radiological and possibly bacteriological manifestations.

The diagnosis of tuberculous primoinfection manifest benignly uncomplicated is based on the diagnostic elements presented above. Bacteriological confirmation is reduced, in 10-20% of cases.

TST is mostly positive; the negative result in a symptomatic child or TB contact requires retesting after 6-8 weeks when the tuberculin turn can be seen that confirms the recent tuberculosis infection.

Chest x-ray is the main screening method in the detection of TB primoinfection in children and allows to highlight the elements of the primary complex. From the radiological point of view, there are several forms of TB primoinfection with benign manifest (figure no. 4 a, b):

- *Unilateral lymphadenopathy*: the most frequent presentation in children (70-80%), hilar or mediastinal lymphadenopathy, without obvious involvement of pulmonary parenchyma, classified as extrapulmonary TB;
- *Typical primary complex (Ranke complex)* is less frequent (20% usually found in children under 5 years), it combines hilar and mediastinal lymphadenopathy and inoculation groove (parenchymal opacity of 3-10 mm with the inferior lobe at the upper lobe or at the base, 1-2 cm above the diaphragm); classification as extrapulmonary TB.

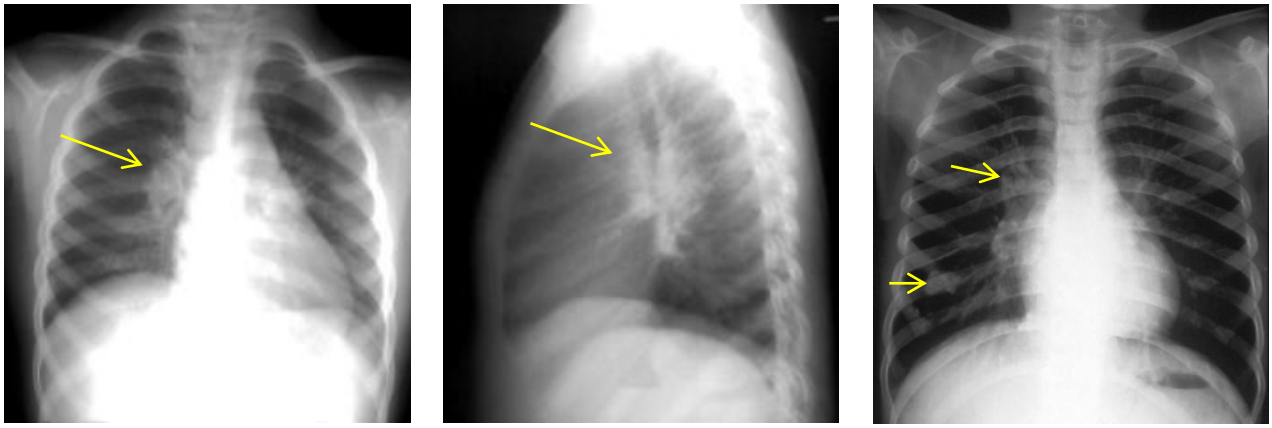


Figure no. 4.(a, b) Radiological forms of Priomoinfection TB manifest benign
a) Unilateral lymphadenopathy b) Ranke complex

B) Manifest TB primoinfection with benign complications is the form of the primoinfection characterized by local complications of the primary complex but with moderate symptomatology. Complications in general are spontaneously regressive, both clinically and radiologically, and are represented by:

- ***Perifocal congestion*** (extensive benign inflammatory processes) represented by condensations that occur around the primary affect or of the lymph nodes, in the form of peripheral reactions;
- ***Systematic inflammatory processes*** - Epituberculosis is presented as tuberculosis infiltrate in connection with the elements of the primary complex as a perifocal reaction (a consequence of tissue hypersensitivity to MTB antigens); sometimes the bacteriological examination is positive and is classified as pulmonary TB;
- ***Bronchial complications in the vicinity*** of tuberculous adenopathy, complications with the potential for aggravation: *Extrinsic ganglionic bronchial compression* with more frequent localization to the middle lobe, radiologically presenting as a retractable opacity (segmental or lobar) with secondary retraction of the diaphragm, fissure or the mediastinum; *Ganglionic-bronchial fistula* is a complication started from the fistulized lymph node with caseum and radiologically a rapid image dynamics is observed;
- ***Serofibrinous pleurisy*** may be a complication of the subpleural primary complex; it is interpreted as a reaction of hypersensitivity, with favorable evolution and complete and rapid resorption, even without adequate treatment;

- ***The primary cavern*** appears in the territory of the primitive outbreak, where the parenchymal infiltrate was, by liquefaction of the caseum and its elimination by a bronchus, when conditions allow it, but it is an extremely rare complication. When the removal of the casein is not permitted, primary casein consisting of a core of solid caseum with a well-organized capsule appears;
- ***Benign hematogenous dissemination***

C) Manifest TB primoinfection with serious complications or *acute tuberculosis* is the form of severe primoinfection that often occurs in the young child with immune deficient and in the case of massive infection and represents the *early complication of the primoinfection* (occurs two to 10 months after the primoinfection). Primoinfection can be followed by massive bronchogenic or lymphohematogenic dissemination, causing severe forms of disease that are the main cause of TB mortality in baby and young children.

From the clinic-radiological point of view, several forms of manifest primoinfection with serious complications are described:

- ***Extensive caseous tuberculosis*** (Pneumonia and bronchopneumonia TB) occurs by bronchogenic dissemination from the elements of the primary complex, usually by ganglion-bronchial fistula; the clinical picture is usually severe and radiologically in case of pneumonia, dense opacities with areas of loss of substance, occupying one or more segments, or even a lobe accompanied by hilar or mediastinal adenopathy. Confluent, inhomogeneous opacities are described in the caseous bronchopneumonia. (figure no. 5-a, b). Bacteriological examination for MTB is frequently positive. These forms of TB are classified as pulmonary TB.
- ***Miliary TB and meningitis TB*** are in the category of extrapulmonary tuberculosis and will be presented in the chapter on extrapulmonary TB.

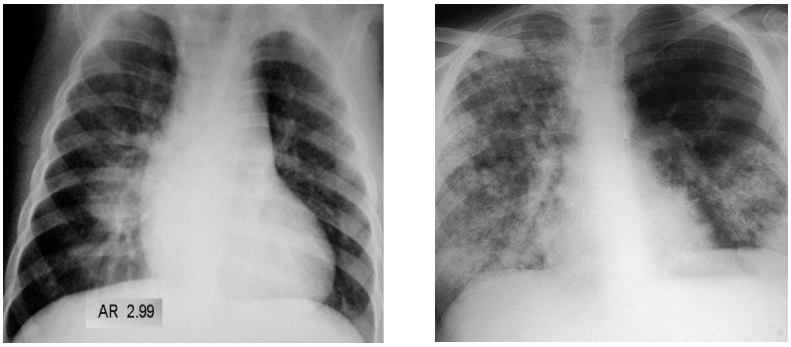


Figure no. 5 a,b. Radiological forms of manifest TB primoinfection with serious complications
a) Pneumonic form ***b) Bronchopneumonia caseous ulcerated***

II. PULMONARY TUBERCULOSIS OF ADULT

Pulmonary tuberculosis of adult or secondary pulmonary tuberculosis (phthisis) is the form of tuberculosis specific to adulthood and may occur either through *the immediate evolution of a primoinfection process*, or as a result of *reactivation of primary tuberculosis* or by *exogenous superinfection* due to a new contact with a source of infection.

Diagnosis of adult pulmonary tuberculosis

Diagnosis of adult pulmonary tuberculosis is based on the *corroboration of the following elements:*

- ***The epidemiological context*** (origin of a tuberculosis outbreak, TB contact, history of incorrect or incomplete TB treated);
- ***Clinical elements*** (which are nonspecific and sometimes absent):
  - ***the clinical onset*** is varied, being: *asymptomatic* (20% of cases), *insidious* (slow, progressive), the most frequent mode of onset, dominated by general symptoms and similarities (encountered in about 40% of cases); *acute* (20%) often encountered in appearance: haemoptoic (20%), flu-like (10-20%), pneumonia-like (5%), pleuretic (rare) or pneumothorax (exceptional); *masked (larval)* extremely rare with dyspeptic, anemic, cardiovascular, endocrine, neurotic manifestations
  - ***general manifestations*** are often the classic *"bacillary impregnation syndrome"* (physical asthenia, anorexia, weight loss - significant at > 10% of the initial weight, predominantly nocturnal sweating and feverish feeling with variable temperature)
  - ***respiratory symptoms*** are dominated usually by *persistent cough*; cough that persists over 3 weeks requires a radiological and / or bacteriological investigation for TB. *The sputum is* usually mucopurulent, in small quantities, but may be absent, especially in women. *Hemoptysis* is relatively frequent, sometimes inaugural (reason for medical consultation); it is usually small (haemoptotic sputum), but it can also be massive, threatening the patient's life
  - ***the thoracic physical examination*** is *relatively poor* (especially in the incipient or localized forms) and is *nonspecific*. Localized cracking rales may be present, especially after cough, located supraclavicular, suprascapular or interscapulo-vertebral; in the forms with endobronchial impairment localized ronflante and sibilant rales may occur. Complete condensation syndrome is rarely and, exceptionally, amphorae breath may be noticed (large cavern, superficially located).
- ***Radiological elements***. Chest x-ray is the central element of the diagnostic approach in persistent cough, but it does not allow to establish the positive diagnosis in pulmonary tuberculosis; The x-ray is not pathognomonic for TB, but only suggestive, thus being an element of diagnostic orientation (not certainty);
- ***Bacteriological examination*** is the only method that can provide the etiologic diagnostic for the disease. The collection of at least two sputum samples, with bacteriological examination for MTB, is mandatory before starting tuberculosis treatment, as effective chemotherapy inhibits MTB growth.

Confirmation of the diagnosis of pulmonary TB is done by isolating MTB from sputum in culture. In the absence of sputum MTB isolation, the diagnosis of pulmonary TB is less certain and implies an evolution under treatment compatible with that of tuberculosis and the absence of an alternative diagnosis**.**

Clinic-radiological forms of pulmonary tuberculosis

Pulmonary TB of adult according to the stages of disease progression has several clinical-radiological forms (figure no. 7.a, b, c):

- ***Infiltrative TB*** is considered the radiological onset of secondary TB, characterized by lesions of exudative alveolitis, radiologically presenting as isolated or partially confluent infiltrates, well delimited or with a narrow contour of the infiltrative-nodular type; Classically, several forms of early infiltrate are described: early Assmann infiltrate, nodular infiltrate, Dufourt nebulous infiltrate, multiple focal infiltrate (plurifocal), and pneumonic infiltrate.
- ***Fibro-caseous TB*** represents the most common radiological form in adults and appears as a result of the unfavorable evolution of an infiltrative tuberculosis. The main characteristic of this form of tuberculosis is cavernous necrosis with *formation of caverns*, radiologically characterized by opacities of all types, infiltrates, cavity lesions, fibrous reparative reactions and areas of emphysema.
- ***Circumcised caseous TB (pulmonary tuberculoma)*** is a relatively rare form, radiologically the appearance is characteristic: round or oval opacity, clearly delimited, costal intensity, usually located in the upper lobes. In 5% of patients it is the only lesion that appears on the x-ray. Tuberculoma may accompany other bacillary lesions (infiltrates, nodules). Sometimes, tuberculomas can be multiple (20%).

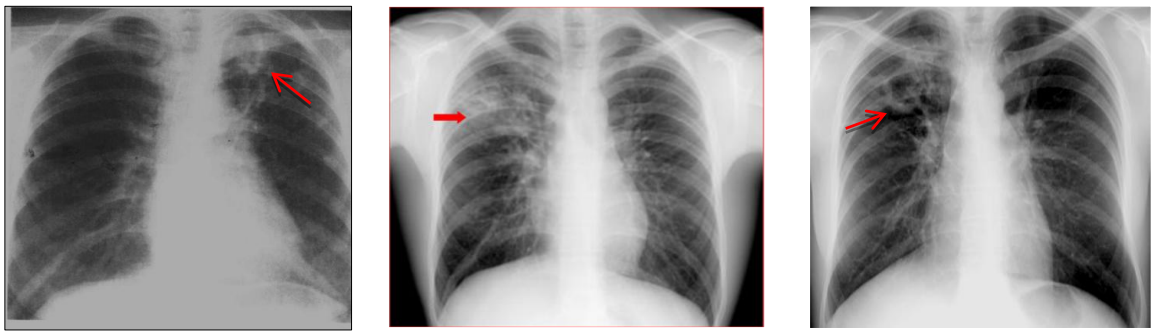


Figure no. 7 a, b, c Radiological forms of secondary pulmonary TB
a) Infiltrative TB b)Fibro-caseousTB c) Cavity TB

Differential diagnosis of secondary pulmonary tuberculosis

The differential diagnosis of secondary pulmonary tuberculosis requires the analysis of two common situations: persistent cough and cavity imaging on the chest x-ray. Less commonly, the differential diagnosis is of a solitary pulmonary nodule (tuberculoma), infiltrative lesions or of a massive pneumonic condensation.

a) Persistent cough (> 3 weeks) occurs in the following situations:

- ✓ *Persistent cough with normal thoracic image* and without other abnormalities has as main causes:
  - Asthma
  - Choric rhinosinusal pathologies (posterior rhinorrhea)
  - Gastro-esophageal reflux
  - Administration of angiotensin converting enzyme inhibitors
- ✓ *Bronchiectasis* usually with chronic mucopurulent bronchore (> 50 mL / day), with repeated episodes of infectious exacerbations; the bacteriological examination is repeated negative for MTB; CT examination reveals bronchial dilation.

- ✓ *Chronic obstructive pulmonary disease* (COPD), historically high smoker, progressive effort, dyspnea, episodes of exacerbation, spirometry with irreversible obstructive syndrome. Bacteriological examination for MTB is not required in most cases.
- ✓ *Lung cancer*-history of high smoking, small hemoptysis, general symptoms, suggestive opacity on chest x-ray, requires endoscopic bronchial examination and CT examination.
- ✓ *Pneumoconiosis*
- ✓ *Mitral stenosis*
- ✓ *Insufficiency of left heart.*

b) ***Radiological lesions.*** The existence of single or bilateral infiltrates, cavity lesions on chest x-ray requires differential radiological diagnosis with a series of diseases (table no. 4).

Table no. 4. Radiological differential diagnosis (TB)

Radiological lesions	**Differential diagnosis**
Unilateral infiltrate	Lung cancer Pneumonia Pulmonary embolism
Bilateral infiltrates	Sarcoidosis Histoplasmosis Coccidiomycosis Extrinsic allergic alveolitis
Solitary cavity lesion	Lung cancer Pulmonary abscess Klebsiella pneumonia Rheumatoid node Pulmonary infarction
Bilateral cavity lesions	Staphylococcal pneumonia Wegener granulomatosis Pulmonary fibrosis

The presence of a ***cavity image*** on the chest x-ray requires a differential diagnostic approach with:

- *Lung abscess* - insidious onset, cough and chronic expectoration, fetid sputum, radiological- hydroaeric image,
- *Lung cancer* - historical smoker, radiological - thick wall cavity ("in the border"), frequently associated with hilar and mediastinal adenopathy,
- *Hydatid cyst evacuated* - historical vomiting with clear liquid, radiological- thin wall cavity, the presence of irregular opacity at the air-liquid interface (proligerous membrane).

The evolution of adult pulmonary tuberculosis

The natural evolution of pulmonary tuberculosis is progressively worsening, with the extent of injury and death in a significant number of cases. The persistence of the sources contributes to the increase of the number of infected persons and to the persistence of the disease in the population.

The evolution of tuberculosis under treatment is slow, radiologically with the resilience of the infiltrates, the reduction in size until the cavities are closed, often localized pulmonary fibrosis, rarely extended; rarely open cavity with thin walls (open cavity syndrome). Complications that may occur during treatment, especially in the fibro- caseous form, are:

- Massive hemoptysis (by erosion of a bronchial artery wall) is rare but potentially fatal;
- Pneumothorax produced by rupture of a cavity in the pleural space, requires surgical drainage;
- Neighborhood pleurisy may accompany lung injury, does not require separate treatment;

Following the cure of tuberculosis, sequelae with consecutive complications may persist:

- Hemoptysis by rupturing the scar aneurysms, the treatment is by embolization and/or surgical excision of the incriminated lesion;
- Bronchiectasis secondary to scar fibrosis; can cause recurrent infectious episodes and/or hemoptysis;
- Chronic respiratory failure secondary to extensive destruction and consequent extensive fibrosis and bronchiectasis;
- Aspergilloma by colonizing Aspergillus fumigatus in a remaining cavity; it can cause hemoptysis and require surgical resection.

EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary tuberculosis (EPTB) is defined as the disease that involves *other locations than those of the pulmonary parenchyma* and represents 1/6 of TB cases in HIV-uninfected adults. It can affect any organ and it does not represent a source of infection.

The origin of EPTB is usually found in hematogenous outbreaks developed during the primoinfection period. The evolution may be *early*, before the primary infection is cured, or *remotely* (even after decades) of primoinfection, by endogenous reactivation.

The general characteristics of the extrapulmonary locations of tuberculosis are:

- general symptoms are less frequent than in pulmonary tuberculosis,
- extrapulmonary lesions are typically paucibacillary which makes bacteriological diagnosis difficult,
- frequently, extrapulmonary locations are difficult to access,
- more frequent in HIV infection, which requires HIV testing in these cases.

The diagnosis of certainty, in the case of EPTB, is often made on the *bacteriological examination* (identification of MTB from pathological products obtained from the affected sites) and/or *histopathological* of the bioptic fragments.

Disseminated tuberculosis (TB miliary)

Disseminated tuberculosis (miliary TB) is caused by hematogenous dissemination during the primoinfection or starting from a reactive outbreak, more commonly extrapulmonary than pulmonary. It can affect any age, both child and young adult.

Miliary tuberculosis is the classic form of disseminated tuberculosis, it is characterized by the presence of numerous small active tuberculosis lesions (under 3 mm) spread throughout the body, most commonly in the lungs, liver and spleen, sometimes in the bone marrow, serous (including meninges), kidneys, central nervous system, adrenals. If the disease is diffuse, and not predominantly pulmonary, the term granulation is still used.

Miliary tuberculosis in children most often is an early complication of primary infection, which occurs in the first 3-6 months after the initial infection, being more frequent in infants and young children (with predilection in the first 3 years of life); it is the consequence of the *lympho-hematogenous dissemination* starting from the elements of the primary complex (usually a caseous adenopathy), very rarely from the active components of the primary intestinal complex (with the digestive input gate). The onset with severe clinical picture developed within a few days is rarely. Most commonly, the onset is subacute and manifests through inappetence, weight loss, fever, general condition alteration.

Miliary TB should be suspected in any child with prolonged fever of unknown etiology, stationary or weight loss, persistent nonresponsive cough at treatment, contact with TB patient, and radiologic-suggestive changes.

Miliary TB in adult is presented clinically as: acute / chronic miliary and disseminated areactiv miliary:

- ***Acute miliary TB*** is a rapidly progressive and invariably fatal clinical form in the absence of efficient treatment. *Clinically: the general intense symptoms* dominate the clinical picture and are nonspecific (fever 38-40^0 C, chills without explanation), intense physical asthenia, anorexia, significant weight loss and relatively rapid *non-productive cough* and later progressive dyspnea until severe respiratory failure, sometimes with severe respiratory failure. acute respiratory distress syndrome requiring ventilator support; *symptoms of other locations*; *the physical examination* shows tachycardia, hepatomegaly and less often splenomegaly. *Chest x-ray may* be normal at the onset of the disease, evolving into a *typical miliary aspect*: bilateral diffuse micronodular opacities. Due to the severity of the disease and the vital importance of the precociousness of the treatment, *the diagnostic suspicion threshold must be very low, and the TB treatment started as soon as possible*.
- ***Chronic miliary TB***, an insidious, more frequent form in the elderly: *Clinical*: fever of unspecified origin associated with consumptive syndrome; *Chest x-ray* shows miliary image. *Diagnosis is difficult*, often postmortem is established.

Tuberculous meningitis

Tuberculous meningitis or TB meningoencephalitis is the acute inflammation produced by the lympho-hematogenic dissemination of the elements of the primary complex at the level of the meninges, superficial cerebral layers and choroid plexuses within the first 6 months or rarely, the dissemination being made later, originating in the lesions of the different intra- or extra thoracic organs. It is common in young children and often occurs in miliary spread tuberculosis in both children and adults.

The diagnosis of tuberculous meningitis in both children and adults is one of probability, given the need for an effective antituberculosis treatment as soon as possible and is based on the epidemiological context and the clinical elements on a series of complementary investigations:

- *the epidemiological context* (contact in family or contact with a patient with pulmonary TB);
- *clinical manifestations* are often nonspecific/uncharacteristic with clinically insidious onset;
- *suggestive clinical elements*: fever, headache, vomiting, cutaneous hyperesthesia, photophobia, redness of the head, neck stiffness, positive Kernig and Brudzinsky signs; sometimes they associate cranial nerve paralysis and / or encephalitis manifestations;
- *tuberculin skin test (TST)* usually negative, but with positive 3-4 weeks after the initiation of the specific therapy (retrospective diagnostic argument);
- *Imaging examination*: *Chest x-ray* shows a variable aspect: normal, miliary image or the appearance of the primary lesion (in the child), *Cerebral CT/Magnetic resonance imaging (MRI)* can present arguments in differentiating tuberculous meningitis from viral, bacterial, fungal or highlighting parenchymal changes in brain tumors (sometimes similar symptoms);
- *examination of the fundus of the eye* can reveal the presence of choroidal tubercles, intracranial hypertension);
- *examination of cerebrospinal fluid (CSF)* obtained by lumbar puncture is *the main diagnostic means: macroscopic* (liquids with clear appearance, or slightly opalescent, hypertensive); *cyto-biochemical* (Pandy reaction strongly positive, cellularity 200-500/mm3, lymphocyte predominance 80-90 %, low glucose, high albumin, low chlorine in CSF); *bacteriologically* (may highlight the presence of MTB); *molecular diagnosis* (GeneXpert Ultra) of mycobacterial DNA detection can greatly increase the diagnostic sensitivity.

Differential diagnosis of TB meningitis is made with other meningitis with clear fluid. When epidemiological and clinic-radiological elements are missing, the diagnosis is largely based on the characteristics of cerebrospinal fluid (Table no. 5).

Table no.5.Differential diagnostic criteria for TB maningitis, CSF

Etiology	Cells/mm^3	Protein mg%	Glucose mg%	Bacteriological examination
Normal CSF	0-5 lymphocytes	20-45	50-75	-
Tuberculous	50-500 lymphocytes	45-50	0-45	Direct examination (-/+) GeneXpert Positive culture in 12-30% cases
Bacterial	500-2000 lymphocytes altered PMNs	50-100	0-45	Germs on direct examination and in culture
Meningococcal	200-500 altered PMNs	Normal	Normal	Meningococcal sediment intra and extra cellular
Viral	0-2000 lymphocytes	Normal or increased	45-100	Negative
Syphilis	10-500 lymphocytes	40-45	15-75	Positive serology
Cryptococcal HIV +	Increased lymphocytes	Increased	Low or normal	Parasites in specific colorations
Meningism	Normal	Normal or increased	Normal	Negative

Tuberculous pleural effusion

Tuberculous pleural effusion is the *most common form of extrapulmonary tuberculosis*. It occurs especially in adolescents and young adults (following a recent infection) and rarely in the elderly (by reactivation).

It is defined as fluid accumulation in the pleural cavity as a result of localization of specific tuberculous lesions at this level and is more probable secondary to rupture of a subpleural pulmonary node than of hematogenous dissemination.

Tuberculous pleural effusion can also appear as a complication of pulmonary tuberculosis in the form of secondary tuberculous pleurisy, sometimes tuberculosus empyema.

Diagnosis of tuberculous pleural effusion in the epidemiological context, on clinical elements and a series of complementary investigations:

- *Epidemiological context* (contact with a case of contagious pulmonary TB)

- *The clinical manifestations* consist of:
  - *onset* that can be: *acute* with intense pleural pain (twinge); they can sometimes be identified by anamnesis and general signs present prior to acute onset (physical asthenia, loss of appetite, weight loss), or *insidious*, especially in adults or the elderly, with chest pain, fatigue, loss of appetite, weight loss and dry cough.

- initially *severe pleural pain (twinge)*, which tends to diminish with fluid accumulation. Patients can take an analgesic position, towards the sick side, to reduce the costal movements.
- *fever* in the case of acute onset, decreases gradually after 2-3 weeks or even faster, while in the case of insidious onset, the thermal ascents are constant, the values being generally below 38 °C. The favorable evolution of fever under tuberculostatic treatment is sometimes the unique or the only etiological argument.
- *cough*, generally dry, is often exacerbated by changing the patient's position.
- *dyspnea with polypnea* which is directly related to the volume of the pleural effusion.

- <u>*The objective examination*</u> reveals a *unilateral pleural fluid syndrome* characterized by intense, disable matity with changing position, associated with the abolition of vesicular murmurs and voice vibrations. When the volume of the fluid is medium, pleuritic breath can be perceived, usually towards the upper limit of the pleural effusion. Pleural rubbing may occur either in the pre-exudative phase (accompanied by pain) or in the resorption period (pain being blurred).

- <u>*Complementary investigations:*</u>
  - *Tuberculin skin test:* initially negative, positive during treatment (retrospective diagnostic argument);
  - *Chest x-ray*: highlights the liquid opacity. In small pleurisy, the costodiaphragmatic sinus obturation is observed. In the pleurisy in the medium quantity, the typical appearance of opacity of mediastinal intensity is observed, homogeneous, stretched, occupying the lower 1 / 3-2 / 3 of the pulmonary field, with the upper edge concave towards the medial and superior, and possibly the movement of the mediastin towards the opposite side. In the massive pleurisies, we observe an intense homogeneous opacity that occupies (almost) the whole hemi-thorax respectively, with the important push of the mediastinum on the opposite side.
  - *Examination of the pleural fluid* obtained by pleural puncture shows a serocitrin fluid, with exudate characteristics (proteins > 3g/L and > 1/2 of plasma proteins, pleural LDH > 2/3 plasma LDH), variable glycopleuria, ratio of pleural lysozyme/ plasma lysozyme > 2, lymphocyte-dominated cytology (> 90%) although neutrophils may predominate in the early stages. Adenosine deaminase (ADA) increased in pleural fluid. These changes are common in tuberculous pleurisy, without being specific.
  - *Bacteriological examination for MTB* in pleural fluid is exceptionally positive in microscopy and rarely in culture (up to 10-15% of cases).
  - *Molecular examination (GeneXpert Ultra test)* of pleural fluid for mycobacterial DNA detection can greatly increase diagnostic sensitivity.
  - *The histopathological examination* from the examination of the pleural fragment, obtained by blind pleural biopsy on the needle or sometimes by thoracoscopy, is diagnosed in 70-80% of cases.

The positive diagnosis of tuberculous pleurisy is based, first and foremost, on *bacteriological and histopathological confirmation,* which together can provide diagnosis in over 85% of cases.

The differential diagnosis of tuberculous pleurisy involves the differentiation of tuberculous pleurisy from other causes of isolated pleurisy. Although there are probability criteria for differentiating tuberculous pleurisy from primitive or secondary neoplastic pleurisy, infectious pleurisy or other etiologies, *confirmation of the diagnosis by pleural biopsy is recommended in all cases.*

The natural evolution of tuberculous pleurisy is usually favorable, with spontaneous resorption and healing with or without sequelae (pahipleuritis, usually limited), but there is a risk of developing pulmonary tuberculosis in the next 3-5 years. Under TB treatment, this risk is prevented, and pleurisy is cured in all cases.

Tuberculosis of the peripheral lymph nodes system

Tuberculosis of the peripheral lymph nodes system is a *common form of EPTB* especially in *children* (over 50% of cases of tuberculosis) and *young adult women.* It is more common in countries with a high prevalence of TB. The mechanism of production is by lymphohematogenic dissemination, the most frequent localization being at the level of the laterocervical and supraclavicular lymph nodes (2/3 of cases), more rarely at the level of other peripheral ganglionic groups and much less at the mediastinal and abdominal level.

The diagnosis of tuberculosis of the lymph node is based on the epidemiological context based on clinical signs and a series of complementary investigations*:*

- *The epidemiological context* can be evocative: contact of TB in the family or entourage;
- *Clinically*, it is characterized by the appearance of localized painless adenopathy (more frequently in the laterocervical and supraclavicular lymph nodes), of elastic or firm consistency, usually not adherent to the adjacent tissues. The evolution is painless, with the appearance of the fluctuation and later fistula with caseum elimination. It is rarely accompanied by general manifestations.
- *Complementary investigations:*
  - *Tuberculin skin test* is frequently positive,
  - *The bacteriological examination for MTB* from the collected caseum, the lymph node or the lymph tissue (obtained by surgical biopsy) *certifies the diagnosis*,
  - *The histopathological examination* of the product collected from lymph node or of the lymph tissue obtained by biopsy completes the diagnosis. Initially, lymph node puncture is recommended, and biopsy is recommended if the result is uncertain.
  - *Molecular examination* (GeneXpert test) from the collected caseum, lymph node or lymph node (obtained by surgical biopsy) for mycobacterial DNA detection can greatly increase the diagnostic sensitivity.

The differential diagnosis is made with non-tuberculous adenitis caused by mycobacteria, with a similar clinical appearance, infectious adenitis of other etiology (staphylococcus, streptococcus, HIV infection), sarcoidosis, malignant lymphomas and neoplasms.

The evolution is favorable under anti-tuberculosis treatment, sometimes with surgical treatment as well.

Osteoarticular tuberculosis

Osteoarticular tuberculosis (OAT), occurs both in children (more often in the first 3 years after primary infection) and in adults, it can be located at any level of the osteoarticular system, but it is located with a higher frequency in the spine (almost half of the cases).

The mechanism of production of OAT is by hematogenous dissemination during the primoinfection in the case of children, and in the case of the adult by dissemination of a recent lung lesion, from an old lung lesion, from childhood or dissemination following a new exogenous infection (the rarest situation); lymphatic dissemination from the pleural cavity to the paravertebral lymph nodes (in the case of vertebral tuberculosis) is less frequent.

At present, there is no way to diagnose osteoarticular tuberculosis quickly and with certainty. Schematically, the *OAT diagnosis involves 5 stages*:

- ***Anamnesis*** with an indicative role may indicate a history of TB or contact with a patient with active pulmonary TB,
- ***The clinic*** characterized by the presence of:
  - *common clinical symptoms* with other non-specific arthritis in the inflammatory phase: joint redness, muscular atrophy, synovial reaction, hydarthrosis, sensitivity to palpation of the joint, local setting,
  - *local signs suggestive for TB*: local swelling, cold abscess, fistula, adenopathy, deformity (kyphosis, flexion stiffness),
  - *general signs of "bacillary impregnation":* weight loss, anorexia, pallor, vesperal low grade fever, fatigue.
- ***Imaging stage:***
  - *Standard radiography* detects the initial signs at 6-8 weeks after the onset of the bone lesion;
  - *Computed tomography* can specify the type of lesion and the extent of the lesions;
  - *Magnetic resonance imaging* brings additional elements to affect the soft parts;
  - *Bone scintigraphy* is predictive in 70% of cases but does not bring additional diagnostic elements.
- ***Laboratory stage:***
  - *The usual laboratory investigations* have only indicative value: increased erythrocyte sedimentation rate (ESR), lymphocytosis in the leukocyte formula,
  - *Tuberculin skin test* can be frequently positive or has tuberculin conversion during the last 2 years.
- *Bacteriological examination for MTB*: direct examination and culture, from pathological products (synovial fluid, para-articular abscesses, bone fragment), is positive only in 25-30% of cases.
- *Molecular examination (GeneXpert test)* of pathological products (synovial fluid, para-articular abscesses, bone fragment) for mycobacterial DNA detection can greatly increase the diagnostic sensitivity.
- ***The histopathological examination*** performed following the bioptic examination of the bone marrow, bone tissue, intra and periarticular structures or satellite lymph nodes, reveals the tuberculous granuloma (follicle).

OAT is a pathological reality the management of this form of tuberculosis is based on a correct diagnosis in orthopedic-pneumologist collaboration, the basic treatment being the medical (pneumological), the surgical treatment (belonging to the orthopedist) addressing only the complications and sequelae.

Urogenital tuberculosis

Urogenital tuberculosis is a rare condition including all the tuberculous lesions located in the urinary and genital tract. The mechanism of production of urogenital tuberculosis is in most cases by hematogenous dissemination at the lung level, but rarely, a tuberculous process of the neighboring structures (spine-tuberculous paravertebral abscesses) can extend to the renal level. At the level of the urogenital tract the organs affected primarily are the kidney and prostate, the other organs being affected secondarily by ascending pathway.

The diagnosis of urogenital tuberculosis can be suggested by: anamnesis (TB contact), clinical symptomatology (general clinical signs of "bacillary impregnation", manifestations of renal / bladder / genital), TST- the result may be positive (argument for diagnosis), paraclinical investigations (usual laboratory investigations and imaging examinations) and confirmed by the histopathological and bacteriological examination by *identifying MTB* from pathological products (urine, menstrual blood); *molecular examination* (GeneXpert test) of pathological products for the detection of mycobacterial DNA can greatly increase the diagnostic sensitivity.

In principle, the treatment is a medical one (anti-tuberculosis treatment), the ablation of any organ imposing itself only in case of its failure or for the resolution of the sequelae.

Tuberculous pericarditis

Tuberculous pericarditis is rare and generally affects older people, with more than half of cases affecting people over 55 years. The mechanism of production of tuberculous pericarditis can be hematogenous (during the initial bacillemia), lymphatic (from a tuberculous adenopathy with caseum) and most commonly by fistulizing a neighboring mediastinal tuberculous adenopathy.

The diagnosis of tuberculous pericarditis is based on the epidemiological context (intrafamilial or entourage TB contact) on a clinical-paraclinical approach:

- *Suggestive symptomatology* represented by signs of dry, exudative or constricting pericarditis,
- *Coexistence of other outbreaks of tuberculosis in the body* (e.g. lung),
- *The tuberculin skin test* is usually positive,
- *The radiographic examination* (cardio-pulmonary radiography or computer tomography) completed by the echocardiographic one shows the quantity of fluid in the pericardial cavity,
- *The pericardial fluid* obtained by pericardial puncture is a sero-sanguinolent or sanguinolent exudate, with an increased cellularity, where mononuclear predominates; *bacteriological confirmation (MTB)* is recorded in 20-30%; *molecular examination (GeneXpert test)* for mycobacterial DNA detection can greatly increase diagnostic sensitivity,
- *Histopathological examination* of pericardial bioptic fragments strengthens the diagnosis.

Other locations

Laryngeal tuberculosis is a rare form, usually associated with extensive pulmonary TB. Clinically, it is characterized by persistent dysphonia (several months), later the general signs similarities of "bacillary impregnation" appear. The evolution is favorable under anti-tuberculosis treatment. Rarely does it cause laryngeal obstruction with the need for a temporary tracheostomy.

Intestinal tuberculosis. Any segment of the intestinal tract may be affected by TB, but the locations most commonly involved are the *terminal ileum and the check*. Pathogenic mechanisms in the production of intestinal tuberculosis are ingestion of sputum with direct sowing, hematogenous dissemination or (rarely) ingestion of milk from cows affected by bovine tuberculosis. Initial symptoms are nonspecific: loss of appetite, weight loss, abdominal pain, chronic diarrhea, bleeding, fistula formation, ascites; there may be one or more abdominal formations, usually easily palpable, and the quantity of fluid in the peritoneal cavity may be so large that no abdominal formation can be felt.

The bacteriological examination of the fluid taken from the peritoneal cavity, of the pus from the fistula, *the histopathological examination* of the fragments collected during the puncture-biopsy of the lymph nodes, intestinal mucosa andor peritoneum (laparatomy / laparascopy) guide the diagnosis.

Peritoneal tuberculosis is more common in women than men and occurs especially in adolescents and young adults. Tuberculous peritonitis may be isolated, only on the peritoneal serosa, but may be associated with the interest of the pleural serosa *(pleuroperitonitis)* or may interest more serous *(pleuro-pericardo-peritonitis or tuberculous polyserositis).* It has an insidious evolution, manifests through ascites without hepatosplenomegaly, sometimes presenting with a picture of acute abdomen. Triad: *ascites + fever + positive TST*, may suggest tuberculous etiology. The diagnosis is often made by exploratory laparotomy with histological and possibly bacteriological examination of the peritoneal fragments collected.

Very rare locations of tuberculosis: *cerebral tuberculomas, cutaneous, hepatosplenic, auricular, ocular, endocrine systems (thyroid, adrenal).*

Treatment of tuberculosis

The goal of anti-tuberculosis treatment is to cure the patient (pulmonary or extrapulmonary) and prevent drug resistance, as well as prevent complications and limit the spread of infection.

Principles of treatment in tuberculosis

The principles that are required to increase the efficacy of anti-tuberculosis therapy and to prevent drug-resistance are:

- ✓ standardized therapy in drug-sensitive TB forms
- ✓ stage therapy (biphasic regimens) in the forms of drug-resistance TB:
  - the attack phase (initial or intensive),
  - the continuation phase (consolidation),

- ✓ combination of anti-tuberculosis drugs (at least three in drug-sensitive forms and at least four in drug-resistance forms);
- ✓ regularity and continuity of medication administration for all duration of treatment;
- ✓ individualized regimens only in the next situations:
  - proven MTB drug-resistance,
  - in case of identification of other mycobacteria,
  - major adverse reactions,
  - associated diseases and drug interactions,
- ✓ no cost for patient – from diagnostic to treatment, including supportive medication, for all TB patients;
- ✓ *the administration of the treatment under direct observation during all the period!!!*

Types of drug-resistance

Depending on the patient's therapeutic history, the following types of drug-resistance are defined:

- ✓ *Primary (initial) resistance* of M. tuberculosis strains detected in patients who have never received anti-tuberculosis treatment and have been infected with drug-resistant bacilli;
- ✓ *Acquired (secondary) resistance* of M. tuberculosis strains detected in patients receiving at least one month anti-tuberculosis treatment;
- ✓ *Monoresistance*: resistance to a single first-line anti-tuberculosis drug;
- ✓ *Polyresistance*, resistance to several first-line anti-tuberculosis drugs, other than Izoniazide and Rifampicin;
- ✓ *Multidrug-resistance (MDR)* is a specific type of polyresistance, defined as resistance to Isoniazid and Rifampicin with or without resistance to other TB drugs;
- ✓ *Extensive resistance (XDR)* resistance to Isoniazid and Rifampicin associated with resistance to any fluoroquinolone and at least one of the second line injectable drugs (Kanamycin, Amikacin or Capreomycin);
- ✓ *Rifampicin resistance (RR):* Rifampicin resistance first detected by genotypic or phenotypic methods, with or without resistance to other anti-TB drugs. Includes any resistance to rifampicin, in the form of monoresistance, polyresistance, MDR or XDR.

Anti-tuberculosis medication

Anti-tuberculosis drugs are traditionally classified in: first-line drugs (essential) and second-line drugs (of reserve). First-line drugs are the most efficient, and least toxic and are therefore included in standard anti-tuberculosis regimens for drug-sensitive tuberculosis forms. Reserve drugs are less efficient and more toxic and are used only in the individualized treatment of drug-resistant tuberculosis.

In the category of anti-tuberculosis drugs, line I are included: Isoniazid, Rifampicin, Pyrazinamide, Streptomycin and Ethambutol, which can be administered both daily and intermittently (Table 7).

Isoniazid (or isonicotinic acid hydrazide) (H, INH) has the most intense bactericidal activity, especially in mycobacterial populations with rapid and extracellular multiplication.

Rifampicin (R, RIF) is also highly bactericidal but has a potent sterilizing effect and is active in all mycobacterial populations.

Pyrazinamide (Z, PZA) is modestly bactericidal but has a potent sterilizing effect, especially on intracellular germs at acidic pH, which is why it is recommended in the intensive phase of treatment.

Streptomycin (S, SM) and ***Ethambutol*** (E, EMB) have modest bactericidal and bacteriostatic effects and have no sterilizing effect.

Table no. 7. List of essential tuberculosis drugs (line I)

Drug	Mode of action	Route of administration	Daily regime (mg/kgc)	Intermittent regime 3x/ week (mg/kgc)
Isoniazid (H, INH)	bactericidal	oral or injectable	5(4-6) to the child 10mg/kgc (7-15)	10(8-15) to the child maximum 300 mg/dose
Rifampicin (H, RIF)	bactericidal	oral or injectable	10(8-12) to the child 15mg/kgc (10-20)	10(8-12) to the child maximum 600 mg/ dose
Pyrazinamide (Z, PZA)	bactericidal	oral	25(20-30) to the child 35mg/kgc (30-40)	35(30-40) similar to the child
Ethambutol (E, EMB)	bacteriostatic	oral or injectable	15(15-20) to the child 20 mg/kgc(15-25)	30(25-35) similar to the child
Streptomycin (S, SM)	bactericidal	i.m	15(12-18) to the child 15 mg/kgc	15(12-18) similar to the child

The reserve drugs are: aminoglycosides (Kanamycin, Amikacin, Capreomycin), thiamides (Protionamide, Ethionamide), fluoroquinolones (Ciprofloxacin, Ofloxacin, Moxifloxacin), Cycloserine, PAS and Clarithromycin and new molecules recently introduced into the tuberculosis drug.

List of reserve TB drugs (line II):
Aminoglycosides: Kanamycin, Amikacin, Capreomycin
Tiamide: Protionamide, Etionamide
Fluoroquinolones: Levofloxacin, Moxifloxacin
Other: Cycloserine, Paraminosalicylic Acid, Clarithromycin, Bedaquiline, Linezolid, Clofazimin, Delamanid

The classification of tuberculosis cases

The case of TB is the patient with tuberculosis bacteriologically or histopathologically confirmed or the patient who does not have confirmation, but at which the pulmonologist decides to start the anti-tuberculosis treatment.

In order to be able to apply standardized therapeutic regimens, a rigorous classification of the different categories of patients is required according to:

a) the chemoresistance spectrum

b) localization of the disease:

Pulmonary tuberculosis **-** if the lesions are in the pulmonary parenchyma, in the tracheo-bronchial arbor or in the larynx. These are contagious forms, important from an epidemiological point of view.

Extrapulmonary tuberculosis **-** if the lesions are in other places than the ones above.

c) therapeutic history:

New case (N) - is the patient who has never been treated with antituberculosis drugs in combination for more than one month. Unconfirmed TB cases can be registered in this category based on the decision of the medical team. When referring to the patient "New case", preventive chemotherapy is not considered.

Retreatment case - is one of the following categories:

- *Relapse (R)* - the patient who has been evaluated as having been cured or completely treated following an anti-tuberculosis treatment and who has a new episode of bacteriologically or histopathologically confirmed TB. The cases of unconfirmed TB can be registered as "relapses" based on the decision of the medical team.
- *Failure retreatment (E)* - the patient who begins a retreatment after having been evaluated "failure" of a previous treatment.
- *Retreatment for abandonment (A)* - the patient who begins a retreatment after having been evaluated "abandonment" or "lost" to a previous treatment and is bacteriologically positive or negative, in which it is decided to resume treatment.
- *Chronic (Cr)* - the patient who starts a new retreatment after having been evaluated "failure" of a previous retreatment.

d) HIV status:

- *The case of TB HIV-positive* is the case with confirmatory or presumptive TB which is HIV-positive at the time of the diagnosis of TB, or on any other previous occasion (previous HIV status must be supported by medical documents such as those certifying antiretroviral therapy).
- *The case of TB HIV-negative* is the case with confirmatory or presumptive TB which is HIV-negative when tested during TB diagnosis. If a subsequent HIV-positive test is found, it will be reclassified.

The case of TB *with two or more locations*, of which at least one pulmonary, will have as main diagnosis the one of the pulmonary localizations, and as secondary diagnosis (secondary diagnoses) that of the extrapulmonary localization. The case will be registered as pulmonary TB.

If none of the locations is pulmonary, the most serious diagnosis will be considered the principal diagnosis, and the other locations will be listed as secondary diagnoses. The case will be recorded as extrapulmonary TB.

Disseminated TB, if it also has pulmonary localization, will be considered as pulmonary localization. The lung anatomical-radiological form will be included in the principal diagnosis, and in the secondary diagnosis the extrapulmonary locations.

The TB of the child will be considered with pulmonary localization if there are lesions of the pulmonary parenchyma, of the tracheo-bronchial arbor or of the larynx (principal diagnosis), respectively with extrapulmonary localization if there are no lesions in these structures (main diagnosis of the single localization or the one of the location of the worst).

Therapeutic regimens

The regimen is made based on: the history of the previous treatments (new case or retreatment), the result of the bacteriological examination (the bacilli are sensitive or not), the form and the extension of the lesions. Group A and B drugs are used for an oral regimen of at least 4 drugs.

Duration of treatment of the disease:

In the forms of tuberculosis with chemosensitivity, *standardized and short-term therapeutic regimens* consisting of two stages are used*: the initial or intensive phase*, when the drugs are administered daily in combination to kill the MTB population in replication and to prevent the development of drug resistance, followed by *the continuation phase*, when the drugs are administered either daily or 3 times a week (as the case may be) in order to annihilate the mycobacterial population with slow or intermittent replication and to prevent relapse (table no.8).

In the forms of tuberculosis with chemoresistance, *individualized therapeutic regimes* are used, with a therapeutic scheme that takes into consideration the patient's therapeutic history, eventual previous contact with a known case with chemoresistance TB, the treatment scheme adapting to obtain maximum therapeutic efficiency. In the design of the individualized therapeutic scheme, the priority therapeutic efficiency is taken into account in the current classification of drugs for chemoresistant tuberculosis (rifampicin resistant, multidrug resistant, extended resistance) is 18 months after obtaining the conversion into cultures (2 negative cultures at two consecutive controls, at least 30 days apart).

In order to initiate individualized therapeutic schemes, it is recommended to consult the MDR Commission (Bucharest or Bisericani).

Table no. 8. Tuberculosis treatment regimens

Treatment regimens	The form of the disease	Association of drugs	
		Intensive phase (7/7)	**Continuation phase**
Regime I	New cases of pulmonary / extrapulmonary TB M(+), M(-)	2 HRZE or 2 HRZS (it will be used in severe pulmonary and extrapulmonary forms) **Obs:** in cases with positive smear at T2: 3 HRZE (S)	4 HR 3 HR **Obs:** in severe cases, the continuation phase is extended to a total treatment duration of 8-12 months*
Regime II	Failure at first treatment Resumption after abandonment Relapse without knowledge DST	2 HRZSE + 1 HRZE **Obs:** reliable antibiograms are required preoperatively and in cases still positive at T3	5 HRE **Obs:** in severe cases, the continuation phase is extended up to a total treatment duration of 12 months *
Regime III	Children suspected or confirmed with peripheral lymph node TB: • living in areas with low HIV prevalence or low Isoniazid resistance, • as well as children who are HIV-negative	2 HRZ	4 HR
Individualized	Known drug-resistant: • Cases of TB RR / MDR / XDR • *Severe side effects to line I drugs* • *Mono / polyresistances* Atypical mycobacteriosis	The drug combinations and the duration of the treatment phases are established by the specialist pulmonologist according to the disease history and DST results.	

DST: drug susceptibility testing, M(+): positive microscopy, M(-): negative microscopy
* The extension of the continuation phase over 4 months (5 months for regime II) or the daily administration in the continuation phase will not be interpreted as an individualized regime

Adverse reactions and their management

Prompt recognition and proper management of adverse reactions is an important part of the treatment program. Toxicity and hypersensitivity reactions require stopping of treatment. It is mandatory to evaluate the adverse reactions and to identify the incriminated drug to avoid stopping some line I drugs (essential).

Depending on the severity of the manifestations the adverse reactions to anti-tuberculosis drugs (essential and reserve) are grouped into *major adverse reactions* that require the stopping/replacement of the responsible drug and *minor adverse reactions* that allow the continuation of the anti-tuberculosis therapy and require dose checking (table no. 9)

Very rarely, the various drugs associated with anti-tuberculosis therapy change the concentration of anti-tuberculosis medication.

Table no. 9. Adverse reactions - TB drugs

Adverse reactions	Medicamente implicate	Suggestions for adverse reaction management	Comments
General reactions			
Anaphylactic reactions	All TB drugs	Exclude other causes. Stop the medication and administer adrenaline 0.2-0.5 1:1000 sc, repeated/ hydration/corticosteroids/ antihistamines; when the symptoms disappear, anti-tuberculosis drugs are gradually reintroduced.	The anaphylactic reaction occurs within minutes of administration of the drug; symptoms: dyspnea, eczema, angiodem, hypotension, fever, shock.
Skin reactions			
Pruritus, rash, erythema, eruptions, dermatitis,	All TB drugs Pirazinamida Clofazimine	Exclude other causes. Medication interrupted may be given antihistamines, local menthol solutions, creams; when the symptoms disappear, anti-tuberculosis drugs are gradually reintroduced.	May occur immediately or up to day 21 from the administration of the drug
Neuropsychiatric reactions			
Convulsions	Clofazimine Isoniazid Fluoroquinolones	Exclude other causes. Initiate anticonvulsant treatment. Reduce the dose of Cycloserine to 500 mg or interruption - then re-enter 250 mg, then 500 mg / day.	Anticonvulsant treatment is continued throughout the treatment or until interruption of the incriminated drug. The medical history with a history of convulsions is not a contraindication to receiving these medications but may be a risk factor for convulsions during DR TB treatment.

Peripheral neuropathy	Isoniazid Injectable (S, Km, Ak, Cpm) Cycloserine Ethambutol Fluoroquinolones	Increase the dose of pyridoxine to 300 mg/day. Multivitamins, physiotherapy, massage Amitriptyline (25-100mg) If it is possible to replace the causative agent, reduce the dose or interrup until improvement. *In severe pain:* - Nortriptyline 25 mg - 150 mg before bedtime - Amitriptyline 25 mg - 100 mg before bedtime - Carbamazepine 200mg - 600 mg	Risk factors – alcohol consumption, underweight, Factori de risc: consum de alcool, greutate scăzută, Diabetes mellitus, vitamin shortages, anemia, HIV infection, renal insufficiency, hypothyroidism. Neuropathy is generally irreversible.
Optical neuritis	Ethambutol Linezolid	Ophthalmologic consultation Interrupt E, Lnz	Reversible at interrupt E.
Anxiety	Cycloserine Fluoroquinolones Isoniazid Protionamida PAS Other factors: Socio-economic circumstances	Anxiolytic treatment	Requires the evaluation of a specialist (psychologist, psychiatrist).
Depression	Cycloserine Fluoroquinolones Isoniazid Protionamida PAS Other factors: Socio-economic circumstances	Psychiatric consultation, psychotherapy. Individual or group psychotherapy. Increase the dose of Pyridoxine to 300 mg / day if the patient is receiving Cs and decrease the dose of Cycloserine. Administrate antidepressants. Temporarily interrup the suspected drug.	Improves socio-economic circumstances. May lead to suicidal ideation (most serious form).
Psychotic symptoms	Cycloserine Fluoroquinolones Isoniazid Protionamida	Administrate antipsychotics. Interrupt the causative agent for a short period (1-4 weeks) until symptom control, then re-enter it in small doses. Psychiatric consultation, psychotherapy. The dose of pyridoxine increases.	Moderate reactions: irritability, anxiety, comportment disorders. Severe reactions: psychoses, depression, suicidal tendencies. Some patients require antipsychotic medication for the entire period of treatment for DR TB. History with a antecedent of psychiatric disorders is not a contraindication for the administration of the drugs involved. Symptoms are usually reversible.

Gastrointestinal reactions			
Dyspepsia Blisters Vomiting Diarrhea	PAS Isoniazid Pyrazinamide Protionamida	Rehydration 1 l NaCl 0.09% iv in the first 12 hours then iv or po. Antiemetic treatment: po with 30 min. before administration of anti-tuberculosis treatment (metroclopramide 10-30 mg) or adm. im. or iv. in severe cases. Doses of the drugs involved decrease. Benzodiazepine combination if the patient is anxious.	Symptoms are common during the first month of treatment and usually disappear when adminis-tering adjuvant drugs. Monitoring of electrolyte levels and their replacement in severe vomiting Symptoms are reversible after dose reduction or interruption of the causative agent.
Gastritis	Protionamida Ethambutol Pyrazinamide Isoniazid PAS	Avoid irritant foods, cigarettes, alcohol. Dose decrease or interrupt the drug involved (1-7 days). Instead, it provides proton pump or anti H2 inhibitors rather than antacids: calcium carbonate, aluminum hydroxide, Mg hydroxide. Performs radiological diagnostic examination, endoscopy.	Symptoms are reversible upon interruption of the suspended drug. Be careful when administering antacids so as not to interfere with the absorption of anti-tuberculosis drugs.
Toxic hepatitis (1x4 NV transaminase growth)	Pyrazinamide Fluoroquinolones Protionamida Isoniazid Rifampicin	Evaluation of liver tests: transaminases increased 4-fold, increased bilirubin - interruption of treatment. Excludes other causes of hepatotoxicity (viral hepatitis B, C). After normalizing the liver tests, the treatment begins again by administering the drugs one by one, the last one being the most hepatotoxic. Change the hepatotoxic drug with the same efficacy.	Risk factors for hepatotoxicity: history of hepatitis, alcohol use, age over 50 years, administration of other hepato-toxic drugs. History of hepatitis antecedents should be carefully analyzed to specify the hepatotoxic agent; this should be avoided in future therapeutic regimens. In general, they are reversible after the stoppage of the drugs involved.

Kidney reactions			
Kidney failure	Injectable (S, Km, Ak, Cpm)	Monitors urea, creatinine monthly. Replace Km with Cpm or decrease doses or interrupt the causative agent. Exclude other causes. If very severe, interrupt all anti-tuberculosis drugs. Re-introduce anti-tuberculosis drugs after normalizing urea and creatinine.	Maximum recommended dose for 6 months, 150 g. Usually reversible to stopping treatment. Risk factors: - doses and duration of treatment, - hypopotassemia, - age, - liver and kidney disease, - concomitant administration of other potentially nephrotoxic drugs.
Reactii la nivelul acusticovestibular			
Vertigo Dizziness Tinnitus Decreased hearing loss to severe hearing loss	Injectable (S,Km,Ak,Cpm)	They may occur at low doses or subsequently by dose accumulation, intermittent administration may delay the onset of the effect.	Very little reversible, it is an invalidating adverse effect that has led to the search for new therapeutic options.

Monitoring of anti-tuberculosis treatment

Monitoring the evolution of the case of tuberculosis under treatment is done:

- *Clinical:* weight gain, weakness, cough disappearance;
- *Biological:* erythrocyte sedimentation rate (ESR), complete blood count, AST, ALT, uric acid, urea, creatinine;
- *Monitoring of adverse effects*
- *Radiological:* it is aimed at reducing the cavities, removing the infiltrates, fibrosis of the nodules;
- *Bacteriological*: at well specified intervals depending on the type of TB case.

The clinical and radiological examination have only an indicative role in the monitoring of the evolution under treatment, and the biological examination shows the tolerance to the anti-tuberculosis treatment.

The periodicity of monitoring the evolution under treatment by bacteriological examination, sputum control (microscopy and culture), is done according to the patient category (table no. 10).

Adverse effects monitoring is an essential parameter for ensuring the success and success of anti-tuberculosis treatment. The identification of adverse effects is primarily clinical, by closely monitoring the patient.

Table no. 10. Periodicity of bacteriological monitoring under anti-tuberculosis treatment

The time of control	New case	retreatment	RR/MDR/XDR*
At the moment of diagnosis	T0	T0	T0
At the end of the initial phase	T2**	T3**	T1
During continuation phase	T4-5	T5	TX
At the end of the continuation phase	T6	T8	

* It is recommended to perform monthly or microscopic examination and cultures for patients with RR/MDR/XDR TB; the antibiogram will not be repeated until after 6 months of maintaining the positivity or at special indications.
** In the case of positivity, it is repeated after one month, during which the intensive phase is continued.

Evaluation of anti-tuberculosis treatment

The initiation of any anti-tuberculosis treatment is followed by the announcement of the case (within a maximum of 48 hours at the TB Dispensary in which the patient lives) and then the case being declared in the territorial and national TB register respectively.

Any declaration of a tuberculosis episode will be followed by a single evaluation, and an evaluation will refer to a single declared TB episode.

The evaluation of TB cases with chemosensitivity and mono / polyresistance is done, the patients are classified in one of the categories: Cure, Completion treatment, Failure, Default, Deceased, Transferred, Lost, Continue treatment

Tuberculosis prevention measures

The measures for the prevention of tuberculosis start from its basic principles as a communicable and socially contagious infectious disease.

Tuberculosis prophylaxis involves a series of specific and nonspecific actions carried out among the population in order to interrupt the epidemiological chain of transmission of the infection from the contagious source to the healthy population and to prevent the appearance of the disease to those already infected.

A) Detecting and treating sources of infection is the best way to prevent tuberculosis. Rapid diagnosis of cases of contagious TB (those with positive microscopy) and the administration of an adequate treatment until cure is the main objective of the control of tuberculosis in a territory and can be achieved by improving the access to healthcare of the all population.

B) ***The measures to reduce the nosocomial transmission of the infection*** are: general measures and special measures (addressed to the worker, the patient and the health unit):

- ***The general measures*** are: administrative, ecological or engineering and the respiratory protection of the personnel. These measures follow: prompt treatment of diagnosed patients, cough hygiene and dilution of bacilli in the atmosphere: efficient ventilation, natural light (solar radiation), ultraviolet radiation.
- ***Special measures***, in the care units of the TB patients (addressed at the same time to the health unit, the workers and the patients) are:

- the implementation at the sanitary unit level of an infection control plan in compliance with the epidemiological circuits,
- hospitalization of patients with pulmonary TB with positive microscopy, in the intensive phase, under suitable habitat conditions. Patients diagnosed with TB will be isolated from patients with other lung conditions; if patients with TB move to common areas or other sections, they will wear surgical masks to prevent air pollution in the areas visited,
- patients with suspected TB-HIV- co-infection will be isolated from the rest of the TB patients, especially those with positive microscopy,
- medical personnel will necessarily use respiratory protection masks, especially in high-risk areas (sputum harvesting rooms, salons with contagious patients, laboratory, during aerosol procedures, bronchology services),
- - the sputum harvesting will be done in specially arranged spaces and containers of single use which are subsequently incinerated,
- adequate natural or artificial ventilation will be ensured for all areas where patients with TB are admitted,
- in the spaces where MDR-TB patients are admitted, air-conditioned hoods and HEPA filters will be placed; wearing respiratory mask for staff is mandatory throughout the activity.

C) Evaluation of TB contacts: the contact investigation is conducted (epidemiological investigation).

TB contact is the person who is close to a patient with contagious TB at a distance which is necessary for a conversation for a minimum of 4 hours.

Epidemiological investigation (EI) is the complex of measures and actions that aims to discover as many people as part of a chain of transmission of TB infection (disease), and the causal relationships between them. Depending on the proposed objective, EI can be:

- ✓ ***Ascending EI*** - is applied when diagnosing a case of TB in the child to identify the source of infection. The main source of TB infection is represented by the patient with a positive pulmonary TB at the microscopic examination in the sputum. Most commonly, the source for the infected small child is intrafamilial, intradomicile, while the source of the older child may be outside the house in the communities they frequent.
- ✓ ***Descending EI*** - triggers the confirmation of any case of pulmonary TB in order to detect the persons (including children) infected or ill from a certain source (index case).

The two types of investigations, ascending and descending, are practically intricate. When the upward investigation discovers the source, it will be treated as a new case, triggering a downward investigation to identify other infected and/or ill cases.

Sometimes it is quite difficult to discover the source, especially in children, since it can be outside their homes. Several tuberculin corners detected in a community of children represent an alarm signal, requiring the triggering of an ascending EI aimed at adults (the staff of the institutions).

D) Prophylactic treatment. The purpose of prophylactic treatment (chemoprophylaxis) is to prevent the development of active tuberculosis in people who have met a source of infection (a patient with positive microscopic pulmonary TB). It is aimed especially at children, adolescents (12-16 years old) and young people (up to 19 years old).

In establishing the indications for the administration of chemoprophylaxis, the criteria for interpreting the skin test for tuberculin, as well as the age and immunity status of the examined person are considered. *The first step is to exclude an active TB!*

Indications for prophylactic treatment (in accordance with PNPSCT recommendations):

- ✓ *newborns from families with TB patient/s;*
- ✓ *children and adolescents up to 19 years old from the TB outbreak:* those with positive TST for at least 6 months; those with negative TST for 3 months, then repeat TST. In case of tuberculin (positive TST) chemoprophylaxis is continued for at least 6 months, and in the case of negative TST, it is interrupted only if the source of contagion (bacteriological or isolation negation) disappears;
- ✓ *adults up to 35 years of age, only in people who have risk factors and have positive TST:* immunosuppressive diseases (leukemias, lymphomas, Hodgkin's disease, acquired or acquired immunodeficiencies); drug immunosuppression (anticancer chemotherapy, steroids); chronic renal failure; pneumoconiosis; poorly controlled insulin-dependent diabetes mellitus; malabsorption syndrome, chronic malnutrition, chronic duodenal ulcer; gastrectomized, especially those with poor nutrition;
- ✓ *persons subjected to anti-TNF alpha immunosuppressive biological therapy, regardless of age, if latent TB infection can be proven.*

Prophylactic treatment of TB drug sensitive cases consists of:

Isoniazid (H) monotherapy, given daily (7/7) 10 mg / kgc / day in children, 5 mg / Kgc / day in adults, (maximum 300mg / day) for 6-9 months for immunocompetents or 9- 12 months for immunocompromised patients (including HIV infected persons). For drug prophylaxis with isoniazid, pyridoxine (vitamin B6), 5-10mg / day in children and 50-75 mg in adults is recommended.

Chemoprophylaxis in drug-resistant TB cases: there are no therapeutic regimens with proven efficacy. Clinical observation is indicated every 3 to 6 months, 2 years after exposure.

D) BCG vaccination is an active immunization method whereby a relative antituberculosis prophylaxis is carried out, which does not prevent infection with M. tuberculosis nor does it interrupt the epidemiological chain of the disease.

Indications of BCG vaccination:

- BCG vaccination offers protection against systemic mycobacterial spreads, such as meningitis and miliary TB,
- in Romania, BCG is obligatory only for newborns. Vaccination is performed in a non-discriminatory manner in all newborns, at the age of 4-7 days (if there are no contraindications), before discharge from maternity and without prior tuberculin testing.
- If the newborn has not been vaccinated in the maternity ward, he/she will be vaccinated until the age of 3 months, without tuberculin testing. In children older than 3 months, recovery for BCG vaccination will be performed only after the advice of the pulmonologist and after prior tuberculin testing, up to 4 years at the latest.

Contraindications of BCG vaccination:

- *temporary:* febrile condition, eruptive skin lesions, weight below 2,500 g;
- *absolute:* symptomatic HIV infection, immunodeficiencies (congenital, leukemias, lymphomas, generalized neoplasms), immunosuppressive treatments with corticosteroids, alkylating agents, antimetabolites, etc.

The BCG vaccination technique must be strictly followed, as indicated in the package leaflet of the biological product used. Otherwise, the risk of post-vaccine adverse reactions (RAPI) is high.

In Romania, BCG vaccination is performed with a strain evaluated periodically for product quality.

BCG (Bacillus Calmette-Guerin) VACCINE SSI is a live vaccine, attenuated by dry freezing for intradermal use. The vaccine should be stored at 2 ° - 4 ° C. The vaccine should be reconstituted with the *saline dilution medium*.

The dosage of the BCG SSI vaccine is:

- ***0.05 ml*** reconstituted vaccine for children <12 months,
- ***0.10 ml*** reconstituted vaccine for children> 12 months and adults.

After 3-4 weeks after vaccination, a small red induration appears, with a diameter of 6-8 mm, which lasts 1-2 months; can ulcerate, eliminating a purulent fluid (caseum). After 2-8 weeks, a crust forms which, after detaching, leaves a round, slightly depressible scar, with a diameter of about 3 mm.

Vaccination is performed only by specially trained medical personnel under the medical and legal responsibility of the physician.

Complications of BCG vaccination are very rare in case of proper vaccination. Exceptionally, axillary or epicondylenic adenopathy may occur, which may fistulize. However, the Calmette-Guerin bacillus can hematogenous disseminate, causing disseminated BCG disease, which has the appearance of miliary tuberculosis upon radiological examination.

Bibliography

1. Global Tuberculosis Report 2018. World Health Organization; 2018
2. Baza națională de date TB: https://81.181.94.7:8080/tb/
3. Adriana Socaci, Georgeta Gilda Popescu, Constantin Marica, "Infecţia tuberculoasă latentă-Întrebări şi răspunsuri" –Ed. Partoş Timişoara 2014. ISBN 978-606-8427-74-4
4. Arghir Oana Cristina, Chiotan Domnica Ioana, Cioran Nicoleta Valentina, Danteş Elena, Homorodean Daniela, Palaghianu Luminiţa Silvia, Popa Cristian George, Popescu Georgeta Gilda, Socaci Adriana, Spînu Victor (autori în ordinea alfabetică). Ministerul Sănătății, Insitutul de Pneumologie ”Marius Nasta” , Programul Național de Control al Tuberculozei. Ghid metodologic de implementare a programului naţional de prevenire, supraveghere și control al tubercu București, 2015. ISBN 978- 973- 139- 325- 4
5. Daniela Homorodean, Adriana Moisoiu. Ghid Național Pentru Rețeaua Laboratoarelor TB. Ministerul Sănătății, Institutul de Pneumoftiziologie ”Marius Nasta”, Programul Național de Prevenire, Supraveghere și Control al Tuberculozei. București; 2017
6. Algorithm for Laboratory Diagnosis and Treatment-Monitoring of Pulmonary Tuberculosis and Drug-Resistant Tuberculosis Using State-of-the-Art Rapid Molecular Diagnostic Technologies: Expert Opinion of the European Tuberculosis Laboratory Initiative Core Group Members for the WHO European Region. World Health Organization, Regional Office for Europe; 2017
7. World Health Organization. Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management. World Health Organization; 2018.
8. Marielna Umbrița Crișan, Elena Barbu. Ministerul Sănătății, Insitutul de Pneumologie ”Marius Nasta” , Programul Național de Control al Tuberculozei. Ghid pentru Managementul Cazurilor de TB La Copii. București; 2017. ISBN 978-606-94469-3-4
9. Guidance for national tuberculosis programmes on the management of tuberculosis in children – 2nd ed. World Health Organization 2014. ISBN 978 92 4 154874 8. www.who.int
10. Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis. World Health Organization; 2018
11. WHO Treatment Guidelines for Isoniazid-Resistant Tuberculosis: Supplement to the WHO Treatment Guidelines for Drug-Resistant Tuberculosis. World Health Organization; 2018
12. WHO consolidated guidelines on drug-resistant tuberculosis treatment. World Health Organization; 2019
13. Strategia Națională de Control a Tuberculozei în România 2015-2020. Guvernul României .http://gov.ro/ro/guvernul/sedinte-guvern/strategia-nationala-de-control-a-tuberculozei-in-romania-2015-2020.

19. PULMONARY EMBOLISM (PE)

Definition

Pulmonary embolism(PE) is the pathological condition defined by the obstruction due to thrombi of the pulmonary arteries or their branches. The thrombi are formed and can migrate from either the profound venous system or the right heart. In rare occasions, the thrombi can develop in situ, inside the pulmonary arteries. It is considered a medical emergency, with potential fatal outcome, dormant or silent clinical manifestations which is the main reason why survival rate of the patients are low.

Epidemiology

The incidence of pulmonary embolism varies from country to country, its variations are due to the accuracy of the diagnosis. In the US alone it is estimated 1case/1000 people/year, value which seemes to be increasing thanks to imaging development and availability across the country. It is believed to be the 2nd cause for sudden cardiac death and the 3rd cause of death in hospital commited patients. At 3 months into the diagnosis, pulmonary embolism (PE) mortality represents 15 % of all reported deaths.

Venous pulmonary embolism (VPE) has 2 clinical forms of manifestation, pulmonary embolism and deep vein thrombosis (DVT), both having same predisposing factors. Pulmonary embolism often appears as a complication to deep vein thrombosis. In 70% of patients with PE there can be proven a presence of DVT. Deep vein thrombosis incidence is higher in women up to 55 years and over 55 years it is most common in men.

Risk factors

Risk factors can be identified in almost 80% of PE cases:

-risk factors pertaining to patient (permanent) and risk factors pertaining to the environment (temporary)

Table 1- PE risk factors *(adapted by European guide for diagnosis and treatment of acute pulmonary embolism, Romanian Journal of Cardiology Vol. 25, No. 1, 2015)*

1. Risk factors pertaining to patient	
Moderate prediction	Weak prediction
• **Hereditary thrombophylia** • **VPE in patients medical history** • **Stroke with loss of mottor function** • **Oral birth control pills** • **Malignancies** • **Estrogon based hormonal treatments** • **Heart failure or chronic respiratory failure** • **intestinal inflammatory diseases** • **Nephrotic syndrome** • **Severe infections, sepsis**	• Advanced age (over 40 years) • Obesity • Pregnancy/ Antepartum period • Varicose veins • Smoking

2. Risk factors pertaining to the enviroment

Strong prediction	Moderate prediction	Weak prediction
• **Major trauma** • **Spine trauma** • **Major general surgery** • **Hip or knee arthroplasty** • **Hip fractures or lower limb fractures**	• Pregnancy/ Postpartum period • Chemotherapy • Frequent central lines • Knee arthroscopy	• Immobilization (more than 3 days in bed, long journeys) • Laparoscopic surgery

There are described many errors in blood clotting and the fibrinolitic system associated with VPE such as isolated anti-thrombin 3 deficiency, C protein deficiency, S protein deficiency, plasminogen deficiency (all clotting inhibitors)

Pathophysiology

The 3 most important factors in thrombi pathogeny (The Virchow Triad – described in 1856) which predisposes the patient to PE and/or DVP are hypercoagulability, hemodynamic changes (stasis, turbulence) and endothelial injury/dysfunction.

Partial and/or total vascular obstruction by thrombi at the pulmonary arteries level have hemodynamic and respiratory consequences. How big of a consequence depends on 4 factors:

- Size of thrombus, extent of obstruction, localizations of the obstruction
- Patients functional cardiac and respiratory status before the PE episode
- Vasoconstriction by release of serotonin, thromboxane, fibrino-peptide B (thrombin-like activity)
- Reflex vasoconstriction (result of pulmonary arteries dilatation).

The most frequent starting point for thrombi to go into the pulmonary circulation is DVT in the lower limb.

The aftermath in pulmonary embolism:

- Local changes in pulmonary tissue and/or pleura (small distal thrombi)
- Changes in respiratory function (shrinkage of the vascular bed in several lobes and/or segments)
- Changes in cardiac function (large thrombi, with over 50% shrinkage of vascular bed, increased activity in right heart)

The respiratory effects of PE are represented by the imbalances between ventilation and perfusion which play a big role in inducing hypoxia. Appearance of un-perfused areas due to obstruction of the vessel leads to creation of shunts to hyper-perfused areas.

The hemodynamic effects like vasoconstriction in the pulmonary circulation and increased pressure in the pulmonary artery (average pulmonary artery pressure is > 40mmHg) lead to overwhelming the adaptive capabilities of the right ventricle followed by right heart failure and sudden cardiac death.

Dilatation of the right side heart cavities with the push of the inter-ventricular septum towards the left ventricle determine right ventricle diastolic dysfunction with systemic hypo-perfusion.

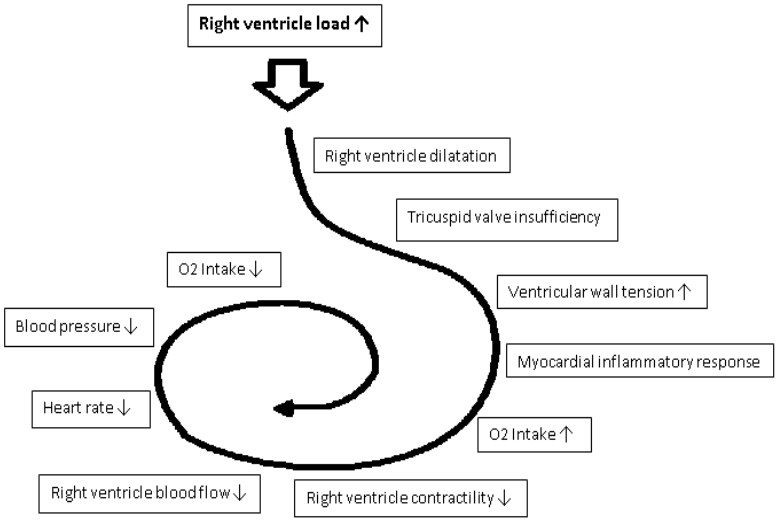


Figure 1. Key factors that contribute to the hemodynamic colaps in PE.

Clinical symptoms

The 3 most common clinical symptoms that make you think of acute episode of PE are *dyspnoea, chest pain and syncope*, symptoms which can appear alone or together.

In **table 2** are described the clinical symptoms according to prevalence and the current guides in literature.

Table 2 - Prevalence of symptoms and clinical signs in patients with confirmed PE

		Prevalence
Clinical signs	**Dyspnoea** – sudden onset thanks to large thrombi assosiated with hemodynamic variations. In patiente with chronic cardiovascular and/or pulmonary disease, increased dyspnoea is the usually the only sign leading to a PE diagnosis	73-80%
	Pleuritic chest pain – present in distal embolisms with small thrombi associated with alveolar hemorrhage or pulmonary infarction	52-66%
	Cough – usually dry, or with mucus expectoration / hemoptic	20-37%
	Syncope: major severe sign, associated with severe hemodynamic variations, low blood pressure, shock. *Iminent death sensation* is offten described in a massive embolism.	19-21%
	Sternal chest pain – angina pain, comes with ischemia of the right ventricle	12-15%
	Hemoptysis – associated with alveolar hemorrhage in cases small embolisms; ussualy in small quantity, may persist over several days	11-13%
Clinical signs	Tachypnoea (> 20 breaths/min.)	68-70%
	Tachycardia (> 100b/min.)	26-35%
	DVP signs – pain, unilateral oedema, congestion in lower limb	11-15%
	Cianosys – in massive embolisms, asociated to right ventricle failure	10-11%
	Fever (> 38,5°C) – apears several hours after the episode of PE	7-11%

Clinical evaluation for diagnosis

There is no direct way to put a diagnosis so there are a few scores for clinical predictions. The most known and commonly used is the one developed by Wells et al. (**Table 3**). It's a simple test based on information that can be easily obtained. Another score similar to this is the revised Geneva score.

Table 3. WELLS SCORE

Elements	Number of points for the clinical diagnosys	
	Original version	Simplified version
History of PE or DVP	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization for at least 4 weeks	1.5	1
Hemoptysis	1	1
Confirmed cancer	1	1
Clinical signs of DVP	3	1
Differential diagnosis more relevant than PE	3	1
Clinical probability		
3 stage scoring system		
Low	0-1	N/A
Moderate	2-6	N/A
High	≥ 7	N/A
2 stage scoring system		
PE not likely	0-4	0-1
PE probably	≥5	≥2
PE probably	≥6	≥3
b/min= beats per minute; DVP = deep vein thrombosis, PE = pulmonary embolism		

Paraclinically diagnosis

Standard chest X-ray – you can see the following aspects (figure 2):

* In half of cases the x-ray is normal (PE suspicion can be made when a patient presents with dyspnoea or hypoxia, without bronchospasm);
* *Hampton sign*: appears after 2 days from infarction debut, presenting necrosis and intra alveolar haemorrhage (triangular opacity with the base facing the pleura, the tip slightly round and convex facing the pulmonary hilum; usually located in the lower lobes);
* *Pleurisy* in small quantity;
* Rising of the hemi-diaphragm;
* *Fleischner sign*: greater diameter in the proximal pulmonary artery, associated with the amputation in the point of thrombus obstruction;
* *Westermark sign*: decrease in pulmonary vascularization in the affected lung thanks to mechanical obstruction and reflex vasoconstriction, seen by increased pulmonary transparency in the affected tissues and the ones with vasoconstriction;
* *Lamelar atelectasis;*

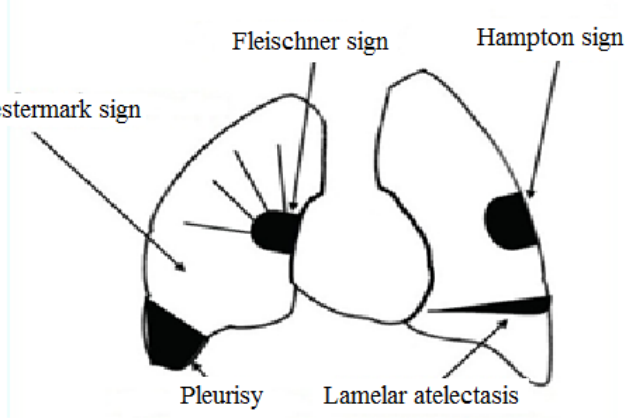


Figure 2 – Different radiological signs

Electrocardiography (EKG)

Useful in patient evaluation in case of dyspnoea and acute chest pain, it can't rule out PE.

You can see: sinusal tachycardia, signs of right ventricle overload: T wave inversed in V1-V4, QR shape in V1. S1Q3T3 is a triad between a extensive S wave in I derivation, a Q wave in III derivation and a T wave reversed in III derivation, associated right branch block (RBD), complete or incomplete. This triad is suggestive, especially in novo cases because it appears only in severe cases of PE of overload in the right ventricle.

Transthoracic echocardiography (TTE)

It is a test of major importance in estimating the risk for pulmonary embolism as well as its hemodynamic consequences.

You can appreciate the following:

-signs of right ventricle dysfunction;
-non-invasive measurement of the pressure in the pulmonary artery;
-presence of thrombi in the pulmonary artery, or right side cavities;

Right ventricle dysfunction is manifested by modifying his capacity (telediastolic diameter right ventricle >3cm or RV/LV ratio >1), paradoxical movement of the interventricular septum, loss of contractility in the free wall versus the right ventricle apex (McConnell sign). During a echocardiography you see this sign associated with modified ejection ration in the right ventricle which is a high prediction factor for EP even when there is underlying cardiopulmonary pathology present.

Pulmonary arterial hypertension (PAH) can be caused by a rapid spike in the systolic blood flow (in pulsatile Doppler) even to its higher value. Short-term increase in pulmonary systolic flow (<70 ms) means a case of severe PAH. Also, quantification in the continuous Doppler mode of the pulmonary regurgitation jet (frequently present in PAH), respectively of the proto-diastolic AP / VD gradient, directs the diagnosis to PAH.

A sign suggestive of acute thromboembolism, the "60/60" sign expressed by a reduced time of increased pulmonary systolic flow (<60ms), to which a trans-tricuspid systolic gradient between 30 and 60 mmHg is added.

The risk of death by PE is doubled when you have the following 2 echographic markers:

- A right/left shunt through patent oval foramen;
- Observing mobile thrombi in the right heart cavities.

Peripheral venous Doppler ultrasonography

It has a sensitivity of > 90% and a specificity of approximately 95% for symptomatic DVT. This method can confirm the presence of DVT in 30-50% of patients with pulmonary embolism.

The diagnosis of proximal DVT in patients with suspected PE is considered sufficient to motivate anticoagulant treatment without further complementary investigations.

In case of suspected EP, Doppler ultrasound can be limited to a simple four-point examination (inguinal and in the popliteal fossa). The only diagnostic principle validated for DVT is the partial compressibility of the vein indicating the presence of thrombus, while flow measurements do not provide diagnostic certainty.

Blood gas parameters

Hypoxemia, hypo- / normocapnia are present, their severity is being correlated with the degree of obstruction caused by thrombi (in the absence of other pre-existing cardiorespiratory conditions).

Normal values of the parameters do not exclude pulmonary embolism.

Laboratory exams

Effective in supporting the diagnosis are the following markers: plasma D-dimers, cardiac troponins and BNP (brain natriuretic peptide) or NT-proBNP (N-terminal prohormone of brain natriuretic peptide). Other biological examinations are non-specific.

Table 4. Biological analysis

Test	Description
Plasma D-dimers	**Values over 500 mcg/L (the cut-off in patients with ages ≥ 50 is : age x 10)** - high levels appear in cases of acute thrombosis by activating coagulation and fibrinolysis - test with negative predictive value - also increased values in situations such as: neoplasms, trauma, hemorrhages, infections, sepsis, necrosis, pregnancy, aortic dissection
Cardiac troponins	- markers for miocardial lesions - elevated at ~ 50% of patients diagnosticated with PE, probably due to miocardial lesions of severe right ventricle overcharge caused by a spike in PSAP, but also due to decreased coronary perfusion, hypoxemia through "mismatch" infusion / ventilation or due to systemic hypotension. - necroptic studies have shown transmural VD infarction with coronary disease, in patients who died from acute PE. - values ≥ 14 pg / ml - at age <75 years, values ≥ 45 pg / ml - age> 75 years are correlated with an increased risk.
Natriuretic peptide BNP or NT-proBNP	- released due to myocardial fiber modifications as a result of VD volume overload - useful in prognostic evaluation - correlated with the severity of hemodynamic impairment and VD dysfunction - patients with increased levels of these samples have an early death risk of 10%, and unfavorable development of 23% in the short term - mortality increases by **6 x for BNP> 100 pg / mL** and **16 x for NT-proBNP> 600 ng / L**

Pulmonary scintigraphy

It was considered the main diagnostic method until recently, but it has lost ground in favor of the tomographic evaluation, being now considered the 2nd imaging method for the diagnosis of PE.

Ventilation-perfusion scintigraphy is a safe, based on the intravenous injection of radiolabeled albumin particles with Technetium (Tc-99m). In a normal examination, there is a warm image, homogeneous and equal capture on both lung areas, but in the case of pulmonary embolism the areas without circulation (due to thrombotic obstruction of the vessel), appear as cold images. To these are added ventilation studies, by inhaling radioactive labeled aerosols (gases), in order to increase the specificity. In pulmonary embolism, ventilation is normal in the hypo-perfused segments

Angiography via CT

- thrombi can be detected from the level of the pulmonary arteries to the level of the segmental arteries;
- the sensitivity of the method is 83% and a specificity of 96% for the multiple detection system (MDCT)).

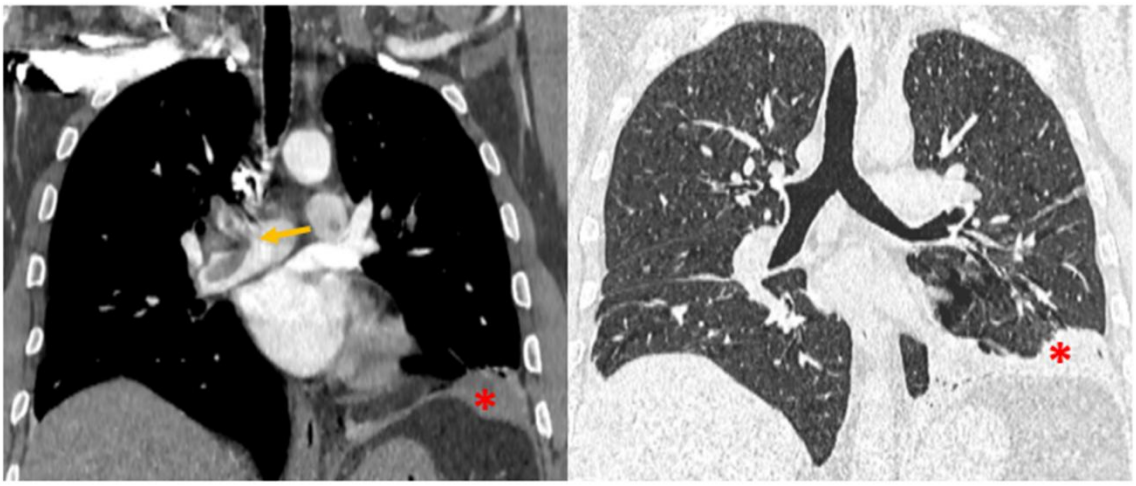
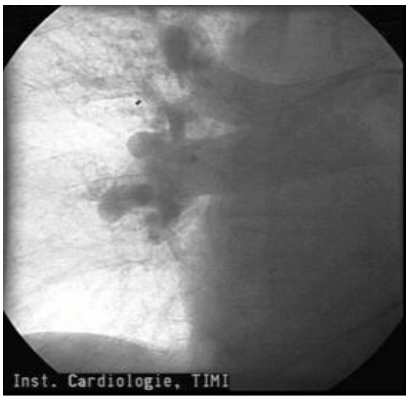
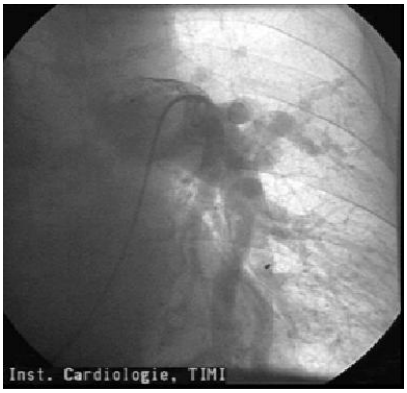


Figure 3. Pulmonary angiography. Defect of intraluminal filling at the level of the bifurcation of the middle and lower right pulmonary artery (arrow). Peripheral pulmonary nodular lesion, hypocaptant with area of microarranging inside, left basal, with characteristic appearance of pulmonary infarction (asterix).

Pulmonary angiography

- is the "gold standard" method for diagnosing or excluding pulmonary thromboembolism,
- the thrombus in the pulmonary circulation is directly highlighted: as a defect of filling or amputation of an arterial branch (**figures 4a and 4b**).
- it is common practice to detect patients who can perform pulmonary endarterectomy.





Figures 4 a and 4 b – Angiographic view in PE

It is, however, an invasive method, the implementation of which requires a catheterization laboratory and qualified personnel. It is considered risk-free: mortality estimated at ~ 0.5%, even higher, in case of hemodynamic instability and respiratory failure.

Right heart catheterism and vasoreactivity testing

Useful in:

- confirming the diagnosis of pulmonary hypertension
- quantification of the severity of the hemodynamic changes
- evaluation of vasoreactivity of the pulmonary circulation

Coronary angiography

Performed in the presence of risk factors for coronary heart disease, angina, if lung transplantation or pulmonary endarterectomy are therapeutic options (patients with chronic thromboembolic pulmonary hypertention).

Prognostic evaluation

Pulmonary embolism severity index (PESI) is a validated score, as a useful predictive method based on clinical parameters. Its advantage consists in detecting patients at low risk of death at 30 days

Another risk stratification method based on the presence or absence of risk markers divides the cases into 3 levels of risk of death (early or late mortality, 30 days after the embolic event).

These markers are:

- clinics: shock and hypotension
- markers of acute right ventricle dysfunction: dilation of the right ventricle(RV), hypokinetic changes of the free wall of the right ventricle or increased velocity of the tricuspid regurgitation jet, ultrasonically highlighted; right ventricular dilatation quantified tomographically; increased BNP or NT-proBNP values; increased pressure in the heart as measured by cardiac catheterization;
- markers of myocardial injury: positive values of troponin T or I

Table 8.

Mortality near the time of pulmonary embolism	Percent	Markers
High risk	**> 15%**	-shoc / hypotension; - RV dysfunction present; - myocardial injury present; Treatment options: thrombolysis or embolectomy
intermediary risk	**3 -15%**	- clinical elements (shock, hypotension) absent; - RV dysfunction present; - signs of myocardial injury absent; Treatment options: hospitalization and specific treatment
Low risk	**< 1%**	- clinical elements (shock, hypotension) absent; - RV with unmodified activity; - signs of myocardial injury absent; Treatment options: early discharge or outpatient treatment.

By the functional class established by the WHO (World Health Organization), according to survival, patients are classified as follows:

- class I - present PHT, with unlimited physical activity; routine physical activities do not induce symptoms such as dyspnea or fatigue, chest pain or pre-syncope.
- class II - PHT present, physical activity is slightly limited, but without the appearance of symptoms at rest; In routine physical activity, dyspnea or fatigue, chest pain or pre-syncope may occur.
- class III - PHT present, light physical activity is profoundly influenced by the appearance of symptoms such as: dyspnea, fatigue, chest pain or pre-syncope, which are absent at rest.
- class IV - PHT present, the symptoms are induced and accentuated by the least effort, the clinical signs of RV insuficiency can be detected; dyspnea and / or fatigue also appear at rest.

Differential diagnosis

Pulmonary thromboembolism is considered the "big mask" for a number of other diseases, because differential diagnosis is laborious and difficult, the symptoms and clinical elements being varied and nonspecific.

• Acute pain: angina, myocardial infarction, pleurisy, pericarditis, dissecting aortic aneurysm
• Sudden dyspnoea: pneumothorax, pulmonary edema, pneumonia, asthma
• Hemoptysis: bronchopulmonary neoplasm, bronchiectasis, pulmonary tuberculosis, Goodpasture syndrome, Angiodysplasia, Mitral stenosis, Pulmonary vasculitis

Evolution

A large percentage of patients with acute PTE survive, 3-month mortality is ~ 15%. In the case of initially severe cases, with shock at the onset, the mortality rate is approximately 7 times higher (in this case death occurs in the first hour from onset).

Complications

On long term, the following may occur:

- Recurrence of thromboembolic events
- Incomplete resolution
- Chronic thromboembolic HTP - incidence 0.1–9.1% in the first 2 years after symptomatic EP event
- Post-thrombotic syndrome

Management / Treatement

I. Treatment in acute fase

A. Hemodynamic and respiratory support

Aggressive perfusion of the patient is not beneficial, this maneuver could lead to the decompensation of the RV function, by the mechanical stretching of the myocardial fibers or by the reflex mechanism of depressing the contractility. However, administration of a small amount of fluid (500 ml) may be useful for increasing the cardiac index in patients with EP, low cardiac index and normal BP(blood pressure). In hypotensive patients, Norepinephrine improves RV function by direct positive inotropic effect, increases coronary RV perfusion, stimulates peripheral alpha vascular receptors, and increases systemic BP.

Dobutamine and / or dopamine may be used in patients with PE, with low cardiac index and normal blood pressure; but the increase of the cardiac index, over the physiological values aggravates the ventilation-perfusion imbalance, by redistributing the flow from the (partially) obstructed to the unobstructed vessels.

Epinephrine, having the beneficial effects of norepinephrine and dobutamine (without systemic vasodilation of dobutamine) can be used in patients with PE and shock.

From small clinical studies, it follows that inhalation of nitric oxide could improve the hemodynamic status and gas exchange in patients with PE. The use of aerosols with Prostacycline in the treatment of HTP secondary EP has been shown to be beneficial.

Clinical studies have also focused on the use of endothelin 1 antagonists and phosphodiesterase-5 inhibitors in pulmonary embolism. In some cases, endothelin receptor antagonization decreased PHT severity due to massive thromboembolic cause, and increased pulmonary artery pressure in experimental EP was slowed by Sildenafil injection.

Hypoxemia is reversible by administration of nasal O2, when necessary, by assisted mechanical ventilation. It must be taken into account that the decrease of oxygen consumption (by reducing fever, agitation), can be resorted to even mechanical ventilation, when the respiratory effort is increased. It also has certain disadvantages in terms of its hemodynamic adverse effects - positive intrathoracic pressure, given by mechanical ventilation, can reduce venous return, aggravating RV insufficiency in patients with massive EP.

The application of positive end-expiratory pressure (PEEP) should be well weighed. Small tidal volumes (~ 6 ml / kg) can be used to maintain a pressure plate at the end of the inspiratory <30 cm H2O.

B. Anticoagulation

It is recommended, in order to prevent both premature death and recurrent or fatal venous thromboembolism, in patients with acute PE.

The standard duration of anticoagulation should be at least 3 months:

- In acute phase, parenteral anticoagulants are administered: unfractionated heparin (HNF), low molecular weight heparin (HGMM) or fondaparinux, for 5-10 days.

- afther that the administration of i.v. heparin overlaps with the administration of vitamin K (AVK) antagonists - or one of the new oral anticoagulants: Dabigatran or Edoxaban.

Another option could be 1-2 days of anticoagulation i.v, followed by oral administration of Rivaroxaban (high dose, 3 weeks) or Apixaban (high dose 7 days)

C. Thrombolytic treatment

This treatment reduces the thrombotic mass, but bleeding complications may occur. It allows to improve the severity of thrombotic obstruction, with functional recovery of RV, especially in patients with hemodynamic instability, with high life-threatening risk.

Table 11. Thrombolytic regimens approved for use in EP

Streptokinaze	250,000 IU, as loading dose for 30 ', then 100,000 IU / h for 12–24 h; ~ accelerated regime: 1.5 million IU for 2 hours
Urokinaze	4,400 IU / kg as loading dose for 10 ', then 4,400 IU / kg / h for 12-24 h; ~ accelerated regime: 3 million IU for 2 hours
rtPA	100 mg for 2 hours or 0.6 mg / kg for 15 '(maximum 50mg / dose)

Contraindications of thrombolytic treatment:

Absolute	Relative
• Hemorrhagic stroke or stroke of unknown etiology (regardless of the time of production); **• Ischemic stroke in the last 6 months;** **• CNS diseases or neoplasms;** **• major trauma / surgery / recent head trauma (within the last 3 weeks);** **• gastrointestinal bleeding in the last month; • known bleeding**	• Tranzitory ischemic injury during the last 6 months; • oral anticoagulant treatment; • pregnancy / first week post-partum; • non-compressible points; • traumatic resuscitation; • refractory HTA (TAS> 180mmHg); • advanced liver disease; • infectious endocarditis; • active peptic ulcer.

D. Surgical embolectomy:

With the bilateral incision of the PA (pulmonary artery), the clots from both branches of the pulmonary artery can be removed.

E. Percutaneous catheter-directed interventional treatment

The purpose of this intervention is to remove obstructive thrombi from the main pulmonary arteries, in order to facilitate the restoration of RV function, followed by the alleviation of symptoms and increased survival.

F. Vein filters:

They are placed in the infrarenal portion of the inferior vena cava (IVC), but if they are in the renal veins, the filter will be placed suprarenaly. The indication of venous filters is in the case of patients with acute PE with absolute contraindications of anticoagulation, as well as in those with confirmed recurrent PE, under appropriate anticoagulant treatment.

II. Long-term treatment

Prevention of medium and long term recurrences

A. Specific treatment for pulmonary hypertension: considered useful in:

- patients with chronic thromboembolic PHT for whom the surgical method is not an option,
- patients in whom the preoperative hemodynamic status can be improved,
- patients with symptomatic recurrent / residual PHT after performing endarterectomy.

B. The long-term anticoagulant treatment aims to prevent recurrent venous thromboembolic events (indications are shown in table 12)

Table 12. Recommendations for long-term anticoagulant treatment in PTE: ***(according to the European Guide for diagnosis and treatment of acute pulmonary embolism, Romanian Journal of Cardiology Vol. 25, No. 1, 2015)***

Situation	Duration
Patients with PTE secondary to a reversible risk factor	Antivitamine K for 3 months
Patients with idiopathic PTE	Antivitamine K for 3 months
Patients with a first episode of idiopathic PTE with stable anticoagulation can be considered for long-term anticoagulant treatment;	Long therm (the risk / benefit ratio is evaluated periodically, maintaining the INR between 2 and 3)
Patients with a second episode of idiopathic PTE	Long therm (the risk / benefit ratio is evaluated periodically, maintaining the INR between 2 and 3)
Patients with PTE and neoplasia	treatment with HGMM 3-6 months, then continuous antivitamin K or HGMM treatment or until neoplasia cures
In patients who refuse or cannot tolerate any oral anticoagulant variant, aspirin may be administered for secondary prophylaxis, long-term VTE	

C. Bilateral lung transplant

It may be considered for patients in whom pulmonary thrombendarterectomy cannot be performed in advanced stages of the disease.

Bibliography

1. Ghidul European de diagnostic si tratament al emboliei pulmonare acute, Romanian Journal of Cardiology Vol. 25, No. 1, 2015
2. Murray and Nadels textbook of respiratory Medicine, sixth edition, 2016
3. Curs de Pneumologie pentru medicii rezidenți, sub redacția Voicu Tudorache, Timișoara, 2013
4. ERS Handbook of Respiratory Medicine 2nd edition, Paolo Palange, Anita K. Simonds
5. Pneumologie, Miron Bogdan, București, 2008
6. Righini et. Al, JAMA 2014, mar 19, 311(11), 1117- 24.doi: 10.1001/jama.2014.2135
7. Kaeberich A et al., ERJ., 2015 G Agnelli., Cecilia Becattini., ERJ., 2015
8. Acute Pulmonary Embolism (Diagnosis and Management of) ESC Clinical Practice Guidelines, 2014
9. Mic tratat de cardiologie – editia a doua, autor: prof. univ. dr. Carmen Ginghina, 2017
10. Compendiu de terapie a bolilor cardiovasculare - Carmen Ginghină (sub redacția), 2017
11. Bertoletti L. The paradoxical association between pulmonary embolism and COPD. Eur Respir J 2017; 50: 1700959 [https://doi.org/10.1183/13993003.00959-2017]
12. Le Mao R, Tromeur C, Bazire A, et al. Risk of recurrent venous thromboembolism in COPD patients: results from a prospective cohort study. Eur Respir J 2017; 50: 1700094 [https://doi.org/10.1183/13993003.00094-2017].

20. TREATMENT OF NICOTINE ADDICTION

Generalities: Smoking is currently present from ancient times in different cultures around the world. If in the beginning was a practice in religious ceremonies after American invasion smoking has spread massively, first cigarettes being manufactured on a large scale in the US in 1860**.** Over time, the perception of cigarettes was from sophisticated to vulgar, from social activity to health hazard. However, in the 50s, it appears the first scientific report reveals the fact that tobacco use is responsible for the emergence of serious diseases. In the meantime, numerous policies for the control of tobacco consumption have emerged in different countries, resulting in a decrease in the number of smokers in developed countries and, in parallel, a new assault from tobacco companies, wishing to occupy the void left by classic cigarette. Thus, "healthy" alternatives appeared like e-cigarette and more recently IQOS.

Definition: Dependence on tobacco is a drug addiction caused by a drug called nicotine. It is associated with daily and long-term consumption of nicotine-based products (cigarettes, pipes, cigars, hookah, chewing tobacco, bidis). Smoker suffering from addictive tobacco can not stop using the substance, even if he knows that it harms. Thus, tobacco addiction is a chronic, recurrent disease that must be properly diagnosed and treated.

Nicotine dependence, according to the WHO, is defined when the patient has a history of chronic consumption with the following characteristics: substance abuse, continued administration of the substance even if negative effects are perceived, high tolerance to the substance and withdrawal symptoms on attempts to cease consumption. It is included in the section "Mental and behavioral disorders caused by the consumption of tobacco" the disease code being F 17 .

Epidemiology: Tobacco consumption is the leading cause of illness and premature death in Europe, each year over 700,000 Europeans dying from smoking-related illnesses. According to Eurobarometer survey published in 2017, 26% of Europeans over 15 years of age and 33% of those aged between 25 and 39 years smoke.

In Romania, according to the same survey, conducted by the European Commission and published on the World Day without Tobacco, tobacco consumption is still relatively high, with a prevalence of smoking 28% in those over the age of 15, close to the European average (26%). Among men, the prevalence is 38% and among women 19% .

Composition of tobacco: cigarette smoke contains over 7 000 toxic constituents, including 50 substances known as potential carcinogens. The most important substances are: nicotine, tar, acetone, arsenic, carbon monoxide, cadmium, hydrocyanic acid, polycyclic aromatic hydrocarbons, nitrosamines, formaldehyde, etc.

Nicotine is the main chemical compound found in tobacco plants that generates addiction. It can be found as a colorless liquid, soluble in water, easily absorbed into the skin and mucous membranes. This is a psychoactive drug that, through repeated use, causes a strong addiction, as pervasive as heroin or cocaine.

The tar is a sticky underlay similar to the resin/tar on the roads , produced by the distillation of various materials: wood, coal, oil, etc.

Carbon monoxide is a poisonous gas similar to smoke that emanates from the exhaust of the cars.

Mechanisms of nicotine addiction: Addiction to tobacco is given by nicotine, which is a substance with psychoactive properties, which increases the acute need to consume tobacco products. The level of addiction induced by nicotine is comparable to that of heroin or cocaine, being able to induce a strong dependence on those people who consume tobacco products chronically.

Once inhaled, nicotine reaches the brain within seven seconds, and attaches to the specific acetylcholine receptors (especially alpha $_4$ beta $_2$ nicotinic acetylcholine receptors) in the area of the accumbens nucleus, which stimulates the release of neurotransmitters, such as dopamine and norepinephrine, thus triggering a "feeling of pleasure". Tobacco consumption will decrease the desire to smoke at the moment, but it will also induce desensitization of nicotine receptors and, at the same time, increase their number, thus increasing the need for the next cigarette. For this reason, tobacco consumers will have to increase the amount of nicotine administered to experience the same intense sensations, thus developing *physically dependency*.

Apart from physical dependence, the repeated use of tobacco products can become a habit, the situations associated with the daily routine as well as the entourage, can increase the consumption of tobacco. Thus we speak of a *psychic addiction* , which, in turn, requires a particular approach.

What makes nicotine withdrawal difficult are the symptoms of *withdrawal* that are manifest within 4 to 12 hours after cessation of use of nicotine, the most common symptoms are: sudden urge to smoke (so called "lust"), irritability, restlessness, anxiety, attention deficit, headache, dizziness, increased appetite, depression. These symptoms differ from patient to patient, as withdrawal phenomena can be very intense.

The clinical diagnosis is based on:

Smoking status:

- Non-smoker: the person who has smoked less than 100 cigarettes in his life (or 100 gr tobacco, in the case of other products)
- Current smoker: a person who has smoked daily for at least three months
- Occasional smoker: the person who smokes, but not daily
- Former smoker: a person who has given up smoking for at least 6 months.

It is recommended that the patient record these data correctly, in order to be able to choose the appropriate strategy for approaching the patient.

The type of product consumed: cigarette, pipe, cigar, hookah, being known that the addiction of cigarette users is faster and is stronger compared to those who consume other products.

The consumption of tobacco is defined as either the number of cigarettes smoked in one day or the number of packs of cigarettes / year (PA number) , which is calculated by multiplying the number of cigarettes packs / day and the number of years of smoking.

Tobacco addiction assessment is done in daily practice by the Fagerstrom addiction test, which divides tobacco users as having low, moderate or high levels of nicotine dependence, the higher the score, the higher the addiction. This score is also useful because it can direct the therapeutic approach of the patient.

1.	When do you smoke your first cigarette after waking up?	
a.	In the first 5 minutes	3
b.	6-30 minutes	2
c.	31-60 minutes	1
d.	Over 60 minutes	0
2.	Is it difficult not to smoke in forbidden places?	
a.	Yes	1
b.	Not	0
3.	Which cigarette do you give up harder?	
a.	First	1
b.	The others	0
4.	How many cigarettes do you smoke per day?	
a.	Under 10	0
b.	10-20	1
c.	21-30	2
d.	Over 30	3
5.	Do you smoke more in the morning than in the afternoon?	
a.	Yes	1
b.	Not	0
6.	Is it difficult not to smoke in forbidden places?	
a.	Yes	1
b.	Not	0
	Total score	

Score:
1-2 - low dependence (no medication needed)
3- 4 - moderate to low dependency (nicotine substitutes can be provided)
5-7 - moderate addiction (combination substitution therapy: patches, gum, tablets)
> 8 - increased dependence (combination substitution therapy: patches, gum, tablets)

Assessment of reason for smoking cessation: after anamnesis, it is important to know what is the motivation of quitting. Most of the time, it is linked to the aspects related to the health of the smoker and to a lesser extent the financial aspects. However, it is proven that less permissive legislation and higher cigarette prices lead to a reduction in the number of smokers over time.

Medical history: Whenever we are in front of a smoking patient, we must also find out his medical history, because many pathologies are triggered or can be aggravated by the presence of smoking.

Paraclinical investigations: tobacco consumption may be objectified by biochemical assays that evaluate the presence of specific biomarkers. These are cotinine (a nicotine metabolite) and carbon monoxide.

Cotinine is the major metabolite of nicotine and can be measured in blood, hair, saliva or urine. Depending on the intensity of smoking, cotinine can reach values of up to 1000 ng / ml, the values of plasma cotinine in non- smokers being below 15 ng / ml. These values vary, being dependent on the time since the last cigarette, bearing in mind that nicotine has a half-life of about 2 hours.

Exhaled CO: is safe indicator for tobacco consumption, but it can be affected by exposure to pollutants from the cooking appliances, defective or non-ventilated heating systems (including gas appliances, charcoal, wood) or faulty exhaust systems. Exposure to CO can be determined by means of a simple and rapid test and the amount of CO is measured in parts per million (PPM), which can be converted to an equivalent of carboxyhemoglobin. In non-smoking individuals the CO value is less than 4 ppm, and smokers, the amount can vary depending on the time of day. As a rule, the values are 10-20 ppm. Half-life of CO is about 4 hours, so that in the mornings the values will lower, after thee sleep break in which no smoking occurred.

Smoking induced pathology:

Cardiovascular disease: although smoking is the cause of cardiovascular morbidity and mortality that is the easiest to prevent by primary and secondary prophylaxis, statistics show complicated that about 20% of the deaths are directly related to tobacco. The probability of such pathology correlates with the number of cigarettes consumed and the period of consumption. For example, studies show that CV disease risk is two times higher in those who smoke one pack / day for 10 years, compared to the a non-smoking patient. The most common conditions are: atherosclerosis, coronary artery disease, strokes.

Respiratory pathology. COPD, lung cancer knowing that smoking is a major risk factor in lung cancer. It also the main trigger / triggers in the production of exacerbations (crises) of asthma by induction of bronchoconstriction and airway inflammation. And regarding tuberculosis, smokers have a 2-3 times higher risk of becoming infected with the bacillus Koch and once infected are more likely to develop the disease than non-smokers, and respiratory infections are more common .

Digestive pathology. Smoking also has an adverse effect on digestive pathology, increasing the risk of gastric and duodenal ulcers, esophageal, gastric, pancreatic and colo-rectal cancer .

Pathology of the female reproductive system. Smoking produces numerous abnormalities of the menstrual cycle: dysmenorrhea, irregular rhythm, secondary amenorrhea. Smoking women have a 50% higher risk of having menstrual pain compared to non-smoking women. It also increases the risk of infertility and early menopause. Cancer pathology is more common in women smokers, cervical and ovarian cancer being more common in smokers. Risk of miscarriage is increased by at least 25% in women who smoke, risk directly correlated with the number of cigarettes; female smokers who use contraceptives have an increased risk of developing deep vein thrombosis and pulmonary thrombembolism.

Pathology of the male reproductive system. Smoking can cause men to lose their libido and sexual potency . Male fertility and erectile dysfunction are also affected.

Pathology of the urinary system. The risk of developing kidney cancer is directly influenced by the dose of inhaled tobacco daily and gender. Also, bladder cancer is more common in smokers.

Effects of smoking on children. Maternal smoking and premature births with malformation risk are closely related(cleft lip), low birth weight, the risk of giving up breast feeding, decreased lung function in children, otitis media in the first year of life and risk of developing obesity. There are also pulmonary problems including asthma, bronchitis, repeated pneumonia. Other conditions that can be influenced by maternal smoking are and intrauterine infections , and sudden death syndrome in children .

Aesthetic changes. Smoking also puts its mark on the skin, determining the premature aging of the skin and the appearance of wrinkles , due to the poor oxygenation of the tissues. Can cause yellowing of teeth, cavities and parodontosis, halitosis and hypersalivation.

Other diseases influenced by smoking: osteoporosis, hip fracture, risk being 41% higher in female smokers, depression, changes in behavior and personality, mood disorders, memory disorders .

General principles recommended in advising smokers: known as the "strategy of 5 A":

Ask (ask): mandatory, during the medical history find out if the patient is a smoker or not, and noted in the observation sheet.

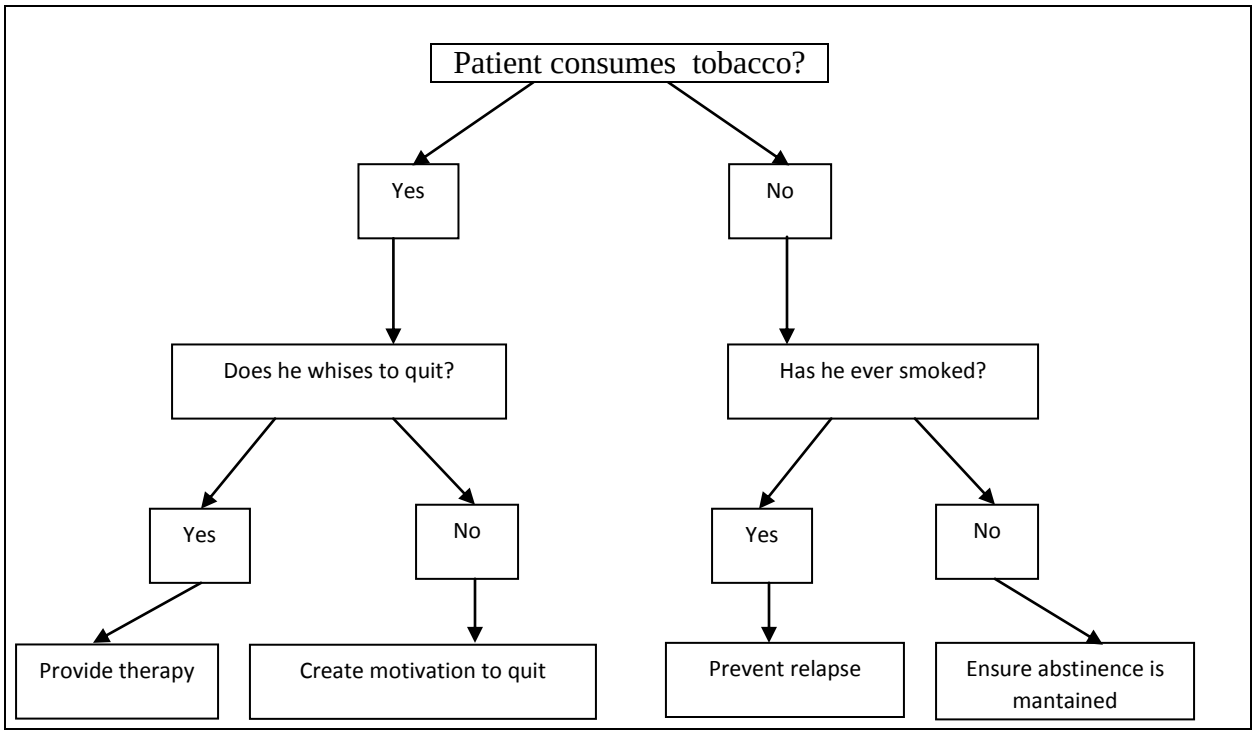
Advise (advise): recommend to each smoker to quit the habit.

Assess (evaluate) should be evaluated the availability of each patient to give smoking and if he already decided give him the necessary informations and possibly therapy. If they are not yet ready, we need to encourage them.

Assist (assist): to patients determined to quit smoking we provide them a specific plan, information, therapy .

Arrange (arrange): set the control visits and in the case of a relapse, assist and support a new smoking cessation plan

Treatment algorithm



Relapse is defined as the resuming of tobacco consumption after a period of abstinence, representing an inevitable part of the recovery process after smoking. Piasecki, shows a common aspect among people who stop smoking: the vast majority of smokers who are enrolled in smoking cessation clinical trials, report a history of quitting attempts, as most of them have already failed at least once while using a pharmacological treatment for withdrawal. Most "falls" occur within the first 24 hours after the day of renunciation.

Tobacco pandemic control

It is done on the one hand by measures that reduce the consumption of tobacco products: prohibition of advertising, direct and indirect, periodically increased prices to all products containing tobacco, the solid legislation to prohibit smoking in public spaces and at the workplace, teaching and information, from the pictures on the cigarette packs to the education and information in schools. These measures have social impact that must be doubled by measures to help smokers quit smoking. Being a chronic disease, nicotine addiction must be diagnosed and a treatment plan must be initiated in order to quit smoking. This plan should combine therapeutic education, behavioral support and pharmacotherapy, where indicated.

Minimum advice: must be performed by all family doctors, dentists, specialist and lasts maximum 3-5 minutes. Must identify smoker status. If the patient does not smoke, he will be encouraged by the doctor to remain non-smoker, and if he was a smoker, encouraged and congratulated for the decision taken.

If the patient is a smoker, he should be encouraged to give up, explaining in clear terms the harmful effects of smoking. If the patient expresses his / her wish to quit smoking in the near future, he / she is directed to a smoking cessation facility for detailed advice.

Although applied individually has little impact with only 1 in 40 smokers opting out, it is more effective than a simple recommendation to quit doubling the rate of withdrawal comparative to lack of any intervention. However, if it is routinely administered as a systematic elementary intervention, minimal counseling becomes a very effective therapeutic tool.

Pharmacological therapy

Nicotinic addiction also benefits from pharmacological therapy, it comprises two categories of medication, first line and second line.

First-line medication:

A. Nicotine replacement therapy (NRT) is a first-line medication recommended to a motivated smokers who wants to quit and to those unmotivated. Using NRT produces a saturation of nicotinic receptors so as to remove the appetite and other withdrawal symptoms, with immediate effect and reduces the number of nicotinic receptors, for several weeks, thus reducing tobacco dependence.

NRT form

a. *Nicotine patches* have the advantage of a more stable concentration, but less effective than oral forms. Nicotine uptake will occur at the skin and subcutaneous tissue level, then reaching the blood and brain. It is very easy to apply and delivers a dose of up to 21 mg / 24 h, in the case of patches recommended for 24 h, or 25 mg nicotine for patches used for 16 h. Common side effects are skin allergy, from mild redness to severe allergic reactions to adhesives.

b. *Nicotine substitutes orally administered:* in the case of oral forms of NRT, nicotine is absorbed in the epithelium of the oral cavity, immediately after chewing and throughout, but also after 15-30 minutes after cessation. Nicotine uptake is possible if the oral pH is neutral, therefore it is recommended to avoid acidic drinks 30 minutes before administering an oral NRT formula.

- *Chewing gum* is sold in concentrations of 2 and 4 mg respectively. Concentration is dictated by the degree of dependence of the smoker. It is necessary to properly administer the gum to be an effective therapy and to avoid side effects, most often these are of digestive nature: pain in the jaws, sores, epigastric pains.
- *Sublingual tablets* are 2 mg or less concentration, uncoated, placed under the tongue and not sucked or chewed. Absorbed in 15-30 minutes and sometimes can cause a sting sensation.
- *Oral tablets,* with doses from 1 to 4 mg, are easy to use, being film-coated tablets that do not require chewing. Oral absorption is better than nicotine gum.
- *Nicotine inhalers* are plastic tubes that contain a nicotine cartridge. They are easy to accept because they support the gesture of smoking.
- *Nasal spray:* it is most effective in suppressing withdrawal symptoms. Can irritate nasal irritation and can maintain dependence because nicotine is given suddenly, like cigarettes .

In conclusion, NRT is an effective medication for quitting smoking, as it has been shown that the combination of oral forms with nicotine patches increases the success rate. Also, the duration of therapy over 14 weeks grows the rate of quitting.

B. Treatment with Bupropion SR

Bupropion is a first-line drug proven effective in quitting smoking. Blocks the neuronal release of dopamine and noradrenaline and, possibly, the action that inhibits the function of nicotinic receptors anticholinergic, proven in vitro.

It is recommended to start treatment with 150 mg Bupropion SR within the first 3 days, then switch to twice daily administration until the end of the 7, 9 or 12 week period.

It is recommended to smokers prone to weight gain, to prevent relapses (it has been proved that extending therapy Bupropion SR leads to an increased proportion of abstinence to 52 weeks), in alcoholic patients who quit smoking and in patients with COPD.

Bupropion therapy is contraindicated under the age of 18, in pregnancy and lactation, allergy to Bupropion or other inactive components, history of convulsive episodes, epilepsy, brain tumors, history of stroke, eating disorders, bipolar psychiatric disorders, alcohol withdrawal, severe liver failure, liver cirrhosis, MAO inhibitors in the last two weeks, benzodiazepine treatment.

Side effects can be frequent insomnia, headache, dry mouth, but can be severe, skin allergy to angioedema, neurological reactions, neuropsychiatric reactions (suicidal thoughts, depression), especially in patients with predisposing risk factors.

C. Treatment with Varenicline

Varenicline is a first-line drug, which by partial antagonism to a4p2 receptors, would promote abstinence from smoking by stimulating dopaminergic neurons and consequently improving the appetite for smoking and nicotine withdrawal . Thus, the satisfaction obtained from smoking and psychological rewards are significantly reduced in patients treated with varenicline.

It is administered orally, the first 3 days 0.5 mg / day, next 4-7 days 2 x 0.5 mg and is continued with 2x1 mg / day until the 12^{th} week.

Contraindications are reduced, hypersensitivity to Varenicline, or inactive components, pregnancy, lactation, age under 18 years. Precautions needed in patients with kidney disease and should be used with caution in drivers and those who handle heavy machinery.

The most common adverse effect is nausea, most frequent in the first week, and lasts on average 12 days. Also mentioned are insomnia, headache and the appearance of abnormal dreams.

Current studies have shown that nicotine patches in combination with oral forms are more effective than a single nicotine replacement product. Also, NRT may be associated with Bupropion but it is not recommended to associate with Varenicline because it acts on nicotinic receptors.

Second-line medication. There are medicines used if first line drugs are contraindicated. These are Clonidine, Nortriptyline and Citizine.

New challenges in tobacco use

Electronic cigarettes are battery-powered devices that heat and emit vapors from a liquid solution that typically contains glycerin, propylene glycol, flavors and additives. This liquid can be found in forms with and without nicotine. It is marketed as an alternative to cigarettes and as a product for smoking cessation. There is not enough evidence about the effectiveness of electronic cigarettes in smoking cessation, so in the absence of them, most national authorities have banned their promotion as an effective means of smoking cessation. There are also studies that have shown that the glycerol vapor is an irritating substance in the event of repeated

exposure, and that aromatic additives can induce oxidative and inflammatory reactions with long-term effects that are difficult to anticipate.

Another recently promoted form of tobacco consumption is IQOS. Through this technology the tobacco is heated but without burning it. Reserves of HEETS tobacco are needed, which mimics cigarettes. It is most often used by smokers as an alternative to indoor smoking, where smoking is prohibited. Although widely touted as a less dangerous form of smoking, the real risks to smokers are still unknown. It is not accepted as a method of quitting smoking.

The most recent studies show that vaping is not harmless at all, being associated with lung diseases that cause death, the common denominator of which is the electronic cigarette. An article published in 2019 showed that the use of electronic cigarettes was associated with pulmonary pathology similar to the pathology caused by exposure to toxic gases.

POLLUTION AND RESPIRATORY CONDITIONS

Gases and particles in the air can increase the risk of a number of respiratory conditions. In the urban environment, people spend over 80% of their time in enclosed spaces, so air quality is a public health issue.

Atmospheric pollutants

The main air pollutants result primarily from domestic activities (table 1).

Outwardly, photo-oxidant pollution is determined, in the summer season, by the effect of solar radiation on nitrogen oxide and volatile organic compounds.

Acid particulate pollution is linked to industrial areas, combustion heating (burning) and car emissions.

The main chemical gases encountered externally include ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and volatile organic compounds (VOC). The particles present in the suspension are a mixture of inert and biological particles, solid and liquid, of different sizes, which we find in the outside air, and can be primary and secondary.

The primary particles can be on the one hand the result of human activities and on the other hand they can be produced by natural phenomena.

The secondary particles are formed in the atmosphere when the gases are changed by chemical reaction.

Particles that pose a risk for respiratory conditions are those that can be inhaled, particles with aerodynamic diameters below 10 microns (called PM_{10}), fine particles with aerodynamic diameter below 2.5 μm (PM_{25}) and ultrafine particles with aerodynamic diameter below 0.1 um ($PM_{0.}$). The particles also contain biological contamination (mites, molds).

In Europe, concentrations of inhalable gases and particles are continuously monitored at urban level, through standardized monitoring devices, which aim to maintain them within acceptable limits, according to protocols.

Main atmospheric pollutants, sources and respiratory effects		
Atmospheric pollutant	**Main sources**	**Health effects and risks**
Outer		
Chemical		
Tropospheric ozone (O_3)	Secondary pollutant resulting from photochemical transformation of VOC and NO_x emitted by traffic, power stations, industrial boilers, refineries or chemical plants in the presence of ultraviolet (UV) rays	Irritation Lung decline Bronchial hyperreactivity Asthma and allergic rhinitis It contributes to the greenhouse effect
Nitrogen dioxide (NO_2)	Road transport (50%), industry (25%), residential (5%), tertiary, urban heating	Disrupts respiratory function Chronic respiratory problems, at high doses can cause injury
Suspended particles (PM)	Road transport (10%), combustion and natural phenomena (volcanic emissions, dust particles, salt)	Respiratory tract irritation Respiratory disorders such as COPD and obstructive ventilatory dysfunction (OVD)
Sulfur dioxide (SO_2)	Industry (80%), residential and tertiary (10%), urban heating	Respiratory disorders At the origin of acid rain
Volatile Organic Components (VOCs)	Road transport, residual and tertiary, solvent use, combustion	Shortness of breath Mutagenic and carcinogenic risk (benzene)
Carbon monoxide (CO)	Road transport (30%), urban heating, residential and tertiary (30%), industry	It disrupts the transphosphorylation of oxygen in the blood: it can cause respiratory problems
Biological		
Allergens, components of volatile microbial organs (mVOC), mycotoxins, viruses, bacteria, etc.	Pollen Humidity in the presence of organic matter (molds, allergens, mVOC, mycotoxins Infectious agents	Allergies: rhinitis, asthma, alveolitis, allergic sensitization mVOC: irritation, rhinitis and non-allergic asthma Other: hay fever, pneumonia, respiratory infections

Inside rooms, the pollutants have two origins: direct emissions and air entering from outside. The most common sources of direct emissions are dependent on their occupants and their activities (smoking, DIY, cleaning), building materials used in home improvement (floors, walls), paintings, insulation materials as well as other equipment in the building (cooking equipment, boilers, air conditioning). Household pollutants are cigarette smoke, particles, nitrogen dioxide, carbon monoxide, volatile compounds, biological allergens. In developing countries, biomass and coal burning for cooking and heating is an important source of pollution. Also, indoor pollutants may also present biological contamination (mites, molds). It should not be overlooked that indoor pollutants are much larger and their concentrations can be much higher than in outdoor air.

Inside		
Chemical		
Cigarette smoke	Tobacco use	Asthma, OVD, COPD, cancer
Polycyclic aromatic hydrocarbons	Cigarette smoke, combustion	Cancer
Volatile organic components (VOCs) (non-methane such as aldehyde and formaldehyde)	Combustion, emission from domestic products (painting, varnish, floors, maintenance products, perfumes and cosmetics, press, cigarette smoke, etc.) Transfer between outside and inside	Respiratory tract irritation, asthma, rhinitis, cancer (formaldehyde)
Suspended particles (PM), PM_{10}, $PM_{2.5}$ or ultrafine	Combustion, heating, cigarette smoke Transfer between outside and inside Cooking with fire	Impaired respiratory function (with lung development difficulties in children)
Nitrogen dioxide (NO_2)	Combustion (gas)	Disrupts respiratory function Chronic respiratory problems
Carbon monoxide (CO)	Incomplete carbon combustion and carbon composite	
Radon	Natural origin	Cancer
Biological		
Allergens	Sources inside the house (mites, pets, etc.) Transfer between outside and inside (pollen, mold (Alteratia ...)	Rhinitis, asthma, allergic sensitization
Molds: allergens, VOCs and mycotoxins	Humidity in the presence of organic matter	Allergy: rhinitis, asthma, alveolitis Other: hay fever, pneumonia
Bacteria, viruses	Transport, air conditioning system (Legionella)	Respiratory infections, pneumonia

Since the 1990s the reduction of industrial emissions has allowed the reduction of acid particulate pollution, but the increase of road traffic has caused a worrying increase of pollution, especially with photo-oxidizing particles, a series of phenomena that lead to the formation of ozone and other oxidizing compounds, from primary pollutants emitted directly into the atmosphere as well as oxidized products and volatile organic compounds (VOCs) as well as energy produced by solar ultraviolet radiation. Also, the chemical pollution inside the dwellings has increased as a consequence of increasing the tightness of the locations to avoid the dispersion of heat and by introducing new chemicals for construction, maintenance, DIY. Climate change is the source of increased exposure to different pollen and mildew.

Atmospheric pollutants can have short- and long-term effects, low at the individual level but not negligible at the population level, for respiratory health indicators such as mortality, hospitalization, respiratory pathologies such as asthma, COPD, lung cancer, respiratory function dysfunction. The effects of prolonged exposure are more difficult to study than those of acute exposure. The role of the tobacco is so important that it becomes difficult to quantify compared to other pollutants.

A few studies have shown that single prolonged exposure to urban pollution can gradually reduce the pulmonary function. Thus, for those who live near a heavily trafficked road a link with asthma and COPD was observed.

Indoor air pollution can increase the risk of irritation, allergic sensitization, acute and chronic respiratory diseases and symptoms and impaired lung function.

In addition to smoking , the internal use of wood and coal are causes of pulmonary pathology. This is especially true in developing countries where individuals are highly exposed. Household products that are a mixture of VOCs have been associated with asthma in both housewives and children whose mothers used them during pregnancy .

Prevention, management of respiratory diseases and respiratory health promotion depends on the clear understanding of the interactions between the individual and potentially harmful agents in the immediately surrounding environment. In the case of atmospheric pollutants , their reduction measures can have a positive impact on health , as can be seen from several real situations . Prevention is effective based on eradicating the sources, reduce emissions and home interior ventilation.

In conclusion, the impact that exposure to chemical and biological pollutants both inside and outside on respiratory health is better due to the evolution of epidemiological methods. An increase in the concentration of atmospheric pollutants, even at low doses, has been associated with excessive risk of mortality and morbidity, as well as impaired lung function and disability. The most consistent results were obtained in the case of particulated pollution. In order to better understand the effect of atmospheric pollutants on respiratory health and to implement more appropriate preventive measures, it will be necessary to develop tools for estimating integrated exposure to pollutants both inside and outside the home, namely exposure to air pollution .

Bibliography

1. International Classification of Diseases (ICD-10). http://www.icd10data.com/
2. WHO. WHO global report: Mortality attributable to tobacco. 2012; ISBN: 978 92 4 1564434
3. European Commission, 2017. Special Euromarometer 458 Report Attitudes of Europeans towards Tobacco and Electronic Cigarettes.
4. Kellar KJ. Neuropharmacology anf biology of neuronal nicotinic receptors. National Cancer Institute, NIH Office on Smoking and Health ^ CDC.
5. Jarvis MJ. ABC of smoking cessation: why people smoke. British Medical Journal, 2004, 328: 277-279
6. West R., Hakek P., Steaad L., Stapleton J. Outcome criteria in smoking cessation trials: a proposal for a common standard. Addiction. 2005; 100 (3): 299-303
7. Benowitz NL. Biohemical verification of tobacco use and cessation. Nicotine Tob Res. 2002; 4: 149-159
8. Jarvis, M. J., Primatesta, P., Erens, B., Feyerabend, C. ^ Bryant, A. Measuring nicotine intake in population suerveys: comparability of saliva cotine and plasma cotinine estimates. Nicotine and Tobacco Research, 2003; 5: 349-355.

9. Risk of cardiovascular disease from cumulative cigarette use and the impact of smoking intensity, Jay H. Lubin , David Couper , Pamela L. Lutsey , Mark Woodward , Hiroshi Yatsuya , and Rachel R Huxley , Epidemiology. May 2016
10. Pharmacological and Chemical Effects of Cigarette Additives, Michael Rabinoff , DO, PhD, Nicholas Caskey , PhD, Anthony Rissling , MA, and Candice Park , Am J Public Health . 2007 November
11. Determinants of cardiovascular disease and sequential decision-making for treatment among women: A Heckman's approach, Raman Mishra , SSM Popul Health . 2019 Apr;
12. Gold Guide 2019 - Global Initiative for Chronic Obstructive Lung Disease https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-FINAL_WMS.pdf
13. Updated guide for asthma management. Practical guide 2008. Guide of the Romanian pneumology company
14. Chiang YC, Lin YM, Lee CN, Chen HY., Tobacco consumption is a reversible risk factor associated with whith reduced successful treatment outcomes of anti-tuberculosis therapy, Int. J. Inf. Dis. 2012; 16 (2) e130-5
15. National Center for Smoking Cessation. Https://stopfumat.eu/fumeful-security/
16. Journal of Radiotherapy ^ Medical. Primary colon cancer: ESMO clinical practice guidelines for diagnosis, adjuvant treatment and follow-up: // https://srrom.ro/wp-content/uploads/2018/04/03.3.2_9_3_Primary_colon.pdf , p. 2
17. Fiore MC, Jaen CR, Baker TB, et al. Treating tobacco use and dependence: 2008 uodate. Rockville, MD: Department of Health and Human Services, US Public Health Service, 2008.
18. Course of pneumology for residents. Mirton Publishing House.Timisoara 2013.pag.324
19. Piasecki TM, Relapse to smoking, Clinical Psychology Review, 2006; 26: 196-215.
20. DeJong W., Relapse Prevention: An Emerging Technology for Promoting Long- Term Drug Abstinence. Substance use and misue, 1994; 29 (6): 681-705
21. Hajek P, Stead LF, West R, Jarvis M, Har tmann-Boyce J, Lancaster T. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews 2013, Issue 8.Art. No .: CD003999.DOI: 10.1002 / 14651868.CD 003999.pub4
22. Taylor M, Leonardi-Bee J, Agboo la S, McNeilA, Coleman T., Cost effectivenyions to reduce relapse to smoking following cessation, Addiction.2011; 106 (10): 1819-26
23. Stead L, Buitrago D, Preciado N, Sanchez G, Hartmann- Boyce J, Lancaster T, Physician advice for smoking cessation. Cochrane Database of Systemic Reviews 2013, Issue 4.
24. Aveyard P, Begh R, Parsons A, West R. Brief opportunistic smoking cessation interventions: a systematic rewiew and meta-analysis to compare advice to quitand offer of assistance. Addiction.2012; 107 (6): 1066-73.
25. Hurt RD, Ebbert JO,, Hays TJ, McFadden DD, Treating Tobacco Dependence in a Medical Setting, CA Cancer J Clin.2009; 59: 314-326
26. Walker N, Howe C, Glover M, McRobbie H, Barnes J, Nosa V, Parag V, Basset B, Bullen C. Cysteine versus nicotine for smoking cessation.N Engl J Med.2014 Dec18; 371 (25): 2353-62
27. West R, Zatonski W, Cedzynka M, Lewandowska D, Pazik J, Aveyard P, Stapleton J.Placebo-Controlled Trial of Cysteine for Smoking Cessation. New Engl J Med.2011; 365 (13): 1192-200
28. Etter JF. The Electronic Cigarette: An Alternative to Tobacco? Geneva, Switzerland: Jean- Francois Etter, 2012; 1-125 , 2012; 141 (6): 1400-6
29. Nayan S., Gupta MK, Sommer DD, Evaluating Smoking Cessation Interventions and Cessation Rates in Cancer Patiens: An Updated Systematic Review and Meta-Analysis, Otalaryngol Head Neck Surg. 2013; 149 (2): 200-11.
30. Cataldo JKDubey S., Prochasja J. Smoking Cessation: An Integral Part of Lung Cancer Treatment Oncology 2010; 78: 289-301
31. Piper M., Smith S.S., Schlam T.R., Fleming M.F., Bittrich A.A., Brown J.L., Leitzke C.J., Zehner M.E., Fiore M.C., Baker T.B., Psychiatric Disorders in Smokers Seeking Treatment for Tobacco Dependence: Relationships Whith Tobacco Dependence and Cessation J Concult Clin Psychol.2010; 78 (1): 13
32. Allen MH, Debanne M, Lazignac C, Adam E, Dickinson LM, Damsa C. Effect of nicotine replacement therapy on agitation in smokers whiz schizophrenia: a double-blind, randomized, placebo-controlled study. Am J Psychiatry.2011; 168 (4): 359-9
33. Fiore M., C., Tobacco Use and Dependence: A 2011 update of CME / CE Treatments.

Pathology of vaping – associated lung injury.Y.M. Butt and others, New Medical Journal, october 2019, DOI: 10.1056/NEJMc1913069

34. ANNESI-MAESANO I, DAB W. Air pollution and the lung: epidemiological approach. Med Sci (Paris), 2006, *22* : 589-594

35. ANNESI-MAESANO I, HULIN M, LAVAUD F et al. Poor ai quality in classrooms related to asthma and rhinitis in primary schoolchildren of the French 6 Cities Study. Thorax, 2012, *67* : 882-688
36. BAYER-OGLESBY L, GRIZE L. GASSNER M et al. Decline of ambient air pollution levels and improved health in Swiss children. Environ Health Perspect, 2005, *113:*1632-1637.
37. CHEN H GOLDBERG MS, VILLENEUVE PJ. A systematic review of the relation between long-term exposure to ambiant air pollution and chronic diseases. Rev Environ Health, 2008, *23*: 243-297.
38. DOMINICI F, McDERMOTT A, DANIELS M et al. Revised analyses of the national mortality and air pollution study: mortality among residents of 90 cities. J Toxicol Environ Health, 2005, *68* : 1071-1092
39. HULIN M, SIMONI M, VIEGI G, ANNESI-MAESANO I. Respiratory health and indoor air pollutans based on measurement exposure assessments. Eur Respir j, 2012, *40* : 1033-1045.
40. JERRETT M, BURNETT RT, POPE CA 3rd et al. Long-term ozone exposure and mortality. N Engl J Med, 2009, *360* : 1085-1095.
41. PENARD-MORAND C, ANNESI-MAESANO I. Maladies allergiques et respiratoires et pollution atmospherique exterieure. Rev Mal Respir, 2008, *25* : 1013-1026.
42. PENARD-MORAND C, RAHERISON C, CHARPIN D et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. Eur Respir J, 2010, *36* : 33-40.
43. ROM WN, SAMET JM. Small particles whith big effects. Am J Resp Crit Care Med, 2006, *173* : 365-366.

21. PULMONARY REHABILITATION

1. DEFINITION. GENERAL INFORMATION

Pulmonary rehabilitation is a comprehensive intervention based on patient assessment, followed by the application of specific therapies, such as physical exercises, education and behavior change of patients, designed to improve the physical and mental status of people with chronic respiratory diseases, as well as to maintain long-term habits that improve symptomatology.

Patients with chronic pulmonary disease have disabling symptoms (dyspnoea, fatigue), limitation of effort capacity, limitation of daily physical activity, all of which affect the quality of life of patients. Moreover, people with respiratory disorders also exhibit extrapulmonary manifestations (skeletal muscle dysfunction, anxiety, depression), which accentuate the symptoms and limit physical activity. Drug treatment is the first-line medication in chronic pulmonary pathology, but sometimes this is insufficient for the adequate control of the symptomatology. In these cases, the pulmonary rehabilitation programs complement the pharmacological therapeutic scheme, in order to improve the quality of life.

The pulmonary rehabilitation program should be individualized according to the patient's needs, based on the assessment of the clinical-biological status, the severity of the disease and the identification of the associated comorbidities. These programs require the contribution of several health professionals, such as: doctors, medical assistants, physiotherapists and nutritionists.

The objectives of the pulmonary rehabilitation program include reducing the symptomatology, maximizing the performance of the physical exercises, increasing the participation in the daily activities, improving the quality of life and modifying the behavior in order to improve and maintain the condition for a long time.

2. ESSENTIAL COMPONENTS OF THE RESPIRATORY REHABILITATION PROGRAM (RRP)

- Patient evaluation;
- Educating the patient (self-management strategies) and family;
- Therapeutic physical exercises (aerobic exercises to increase muscle strength and tonicity);
- Re-education of breathing;
- Adequate medical-surgical treatment;
- Prevention and management of respiratory infections;
- Psycho-social support;
- Correct use of oxygen therapy systems;
- Nutrition assessment;
- Bronchial drainage techniques;
- Quitting smoking;
- The correct understanding of the inhalation techniques of the medication.

3. PULMONARY PATHOLOGY to which the initiation of a RRP is expected

Obstructive pulmonary disease: chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, cystic fibrosis.

Restrictive pulmonary diseases: interstitial pneumopathy (pulmonary fibrosis, occupational pulmonary pathology), sarcoidosis, thoracic wall deformities (scoliosis, kyphosis), neuromuscular diseases with pulmonary impairment, respiratory diseases due to obesity.

Other respiratory pathologies: pulmonary hypertension, lung cancer, pulmonary pre/post-transplant, reduction of lung pulmonary volume, autoimmune diseases with pulmonary impairment, pre/post thoracic or abdominal surgery.

4. INDICATIONS AND CONTRAINDICATIONS

Pulmonary rehabilitation is recommended for all patients with chronic pulmonary pathology, with symptoms present and limitation of daily activity, despite the use of appropriate pharmacological therapy. The pulmonary rehabilitation program can be initiated at any stage of the disease, during the period of clinical stability, during exacerbations or after stabilization of an exacerbation.

The primary *contraindications* for starting a RRP are:

- The presence of a condition that could interfere with the rehabilitation process, such as severe neurological, cognitive or psychiatric illnesses, disabling arthritis;
- The association of a comorbidity that could endanger the patient's life during training - severe pulmonary hypertension or unstable cardiovascular disease.

The lack of motivation, desire of the patient to participate in a RRP is considered a relative contraindication; the level of motivation may change during therapy, especially if patients perceive benefits (improvement of clinical status) during respiratory recovery sessions.

Age or degree of pulmonary impairment are not criteria for inclusion or exclusion in a PRP, these pointing to a particular type of PRP. It is necessary to perform a maximum effort test to identify possible contraindications, as well as to identify the intensity of the training.

To complete a RRP it is very important that patients are willing and able to learn about their disease and are motivated to give time and effort to take on such a program.

5. TYPES OF LUNG REHABILITATION PROGRAMS

RRP requires a long running time of at least 6-8 weeks, which is why these programs need to be as flexible as possible, individualized and adapted to the disability type of the patient.

Types of RRP:

- *"In patient"* - patients are admitted to a specialized institution for various causes, such as: they have great disabilities, they are unable to go to a RP center or they are in an unstable phase of illness (convalescence).
- *"Out patient"* - outpatients who come regularly to rehabilitation sessions in a specialized center; this program can also function as a day hospital, with multiple presentations; patients should be encouraged to carry out physical training at home alone between sessions at the center.
- *"Home patient"* - the qualified personnel offers medical rehabilitation assistance at the patients' home.
- *"Community rehabilitation"* - this type is represented by sports centers, gyms or medical centers, located in the home area of a group of patients.

Each of these types of RRP has certain advantages and disadvantages, which we will present in table 1.

TYPE OF PROGRAM	**BENEFITS**	**DISADVANTAGES**
In-patient	Intensive. It confers safety.	High cost. Limiting family access.
Out-patient	Saving medical resources compared to the "in-patient" type. It confers safety.	Move to RP center. Limited number of patients.
Home patient	It offers the possibility to remain in the environment with which the patient is accustomed. It does not require moving to the PR center. Many patients may be included. Low cost.	It is important for the patient to be motivated. Absence of group-related stimulation. Absence of therapeutic education. Lack of adequate monitoring.
Community rehabilitattion	Close to home. Development potential.	Staff availability. Quality of supervision.

Table 1. Advantages and disadvantages of different types of RRP.

The duration of a RRP is not precisely established. The duration varies depending on the complexity of the case and the possibilities of the rehabilitation center. In general, it takes at least 6 to 8 weeks with 2 to 3 sessions per week (a cumulative duration of 72 hours) to obtain favorable effects on physical performance and quality of life. The duration of the sessions per week is approximately 150 minutes distributed as follows: 60 minutes are allocated to medical education (explanation of anatomy, medication, nutrition, etc.) and 90 minutes are allocated to physical exercises. The duration is not fixed, depending on the type of program and the complexity of the disease.

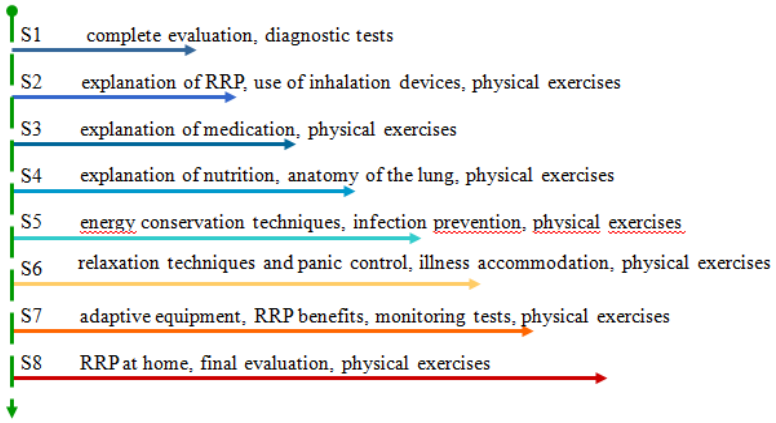


Figure 1. The sequences and content of each respiratory rehabilitation session.

6. PHYSICAL TRAINING

Patients with chronic respiratory disease, especially those with COPD, have dyspnoea and fatigue that limit their effort capacity and affect their quality of life. This symptomatology is due to several factors, of which we mention: skeletal muscle dysfunction, impaired pulmonary gas exchange, cardiac dysfunction.

The affected skeletal musculature plays an important role in the appearance of symptomatology in these patients. Thus, the improvement of muscle function through aerobic training improves the effort capacity of the patients, even if the values of the functional lung tests do not improve.

Factors that cause altered skeletal muscle function are:

- Sedentarism / physical deconditioning;
- Systemic inflammation;
- Malnutrition;
- Oxidative stress;
- Tissue hypoxia;
- Old age;
- Smoking;
- Hormonal disorders (insulin resistance, decreased testosterone level);
- Individual susceptibility;
- Use of corticosteroids.

Physical training is considered the cornerstone in the process of improving muscle function. To stop the destruction of muscle mass, physical training must be well individualized and rigorous.

The metabolic and structural changes that occur in the muscles secondary to physical exercises are:

- The proportion of type I and II fibers changes - the percentage of type I fibers increases;
- Capillarization is improved;
- Increases myoglobin level;
- Improves oxidative capacity - reduces lactic acidosis, decreases CO_2 production, delays the appearance of muscle fatigue and decreases the intensity of the perception of muscle effort.

In recent years, more and more emphasis has been placed on evaluating the patients' ability to perform activities of daily living (ADLs). Daily physical activity and therapeutic physical exercises slow down the course of the disease, delay the installation of chronic diseases (osteoporosis, atherosclerosis) and increase survival. Limitation of ADL in people with chronic lung disease reflects muscle deconditioning and the presence of limiting symptoms. Although inactivity is seen as a cause of the disease, it contributes to the progression of physical deconditioning and symptoms aggravation, thus creating a vicious circle.

ADL quantification is done by subjective methods (questionnaires assessing dyspnoea, household activities, physical limitations etc.): CRQ (chronic respiratory disease questionnaire), SGRQ (St. George's respiratory questionnaire), SOBQ (shortness of breath questionnaire), QLI (quality of life index), SPF (satisfaction of physical functioning), PASE (Physical Activity Scale for the Elderly), etc.), as well as by objective methods (pedometers, accelerometers). Pedometers record only the number of steps per day, week or month, while accelerometers allow quantifying the amount and intensity of motor activity.

Muscle dysfunction is quantified by various tests. The respiratory musculature is evaluated by determining the maximum inspiratory pressure (PImax) and the maximum expiratory pressure (PEmax). The peripheral musculature (upper and lower limbs) is evaluated by dynamometry and the 6-minute walking test (it quantifies the capacity to exercise), and the body composition is evaluated by bioimpedance.

It is important that physical training is aimed primarily at the muscle groups involved in the patients' daily activities. Thus, during the rehabilitation sessions, it is important to work the muscles of both the lower limbs and the upper limbs. The trainings aim to improve the muscle function, coordination, balance, posture and the most efficient daily activities.

To improve the muscles of the lower limbs, walking with stairs, swimming or cycloergometry will be associated. The upper extremity can be trained in different ways, from using hand weights to accessing resistance circuits. The loading should be carefully dosed and supervised, especially in the elderly and those with corticosteroids, to avoid the risk of muscle or tendon rupture and fractures.

Strengthening the musculature of the core by lifting and pulling back the shoulders, associated with the increased flexibility of the pectorals helps maintain a normal posture, thus improving respiratory mechanics.

Bronchodilator therapy should be adjusted as it will allow patients to exercise at higher intensities. Similarly, oxygen therapy is indicated for hypoxemic patients, thus increasing their safety and ability to perform exercises at a higher level.

Electrostimulation and ventilator support are indicated for severe cases.

7. RRP EFFICIENCY ASSESSMENT

RRP efficiency or non-efficiency is quantified by periodically monitoring the parameters obtained at the initial patient's assessment. Among them we mention the monitoring of the lung function, the assessment of effort tolerance, symptomatology, quality of life, nutritional status and daily life activities.

Pulmonary rehabilitation programs have proven to be effective in all of the above mentioned RRP categories, but most of the results published in the specialized literature, have been carried out in specialized centres and have used *in-patient* or *out-patient* programs.

It is considered that a RRP performed over a period of 1.5-3 months was effective if:

- An increase in the effort capacity is quantified by:
  - The walking test improved by 10-25%, which corresponds to 50-80 meters;
  - An endurance of at least 10 minutes is obtained when performing on the treadmill or at least 5 minutes at the cycloergometer, performed at submaximal effort;
  - Increases the maximum oxygen consumption (VO2max);
  - 30 minutes duration of endurance/session of the respiratory musculature subjected to an effort of 30-35% of the maximum inspiratory pressure (PImax);
  - For the same intensity of physical exertion there is a reduction of ventilation, lactacidemia and an improvement of the oxidative enzymes' activity.
- Reduces the sensation of dyspnoea during the effort.
- Weight gain > of 2 kg in 8 weeks is recorded in the underweight patients.
- There is an improvement of the quality of life, quantified by the decrease by ≥ 4 points in the SGRQ questionnaire or the increase by ≥ 0.5 points in the CRQ questionnaire).

8. THE BENEFITS OF RRP

An effective pulmonary rehabilitation program has the following benefits for the patient:

- Reduces the symptoms (dyspnoea and fatigue);
- Increases effort capacity;
- Increases the ability to carry out daily life activities;
- Improves the quality of life;
- Reduces anxiety and depression;
- Improves sleep quality;
- Improves lipid profile;
- Reduces systemic blood pressure;
- Provides additional knowledge to the patient regarding the disease and treatment;
- Reduces the number of hospitalizations and implicitly the use of medical resources;
- Reduces premature mortality.

The benefits of RRP accepted by most authors are the improvement of the symptomatology, the increase in effort tolerance and the quality of life improvement. The benefits of rehabilitation sessions are higher in *out-patient* RRPs compared to *home-patient* ones.

The duration of the benefits depends on the patient's compliance and the readiness to acquire a new way of life. In the absence of a physical training maintenance strategy, RP benefits appear to decrease in 6-12 months. The reasons for this decline are multifactorial, including decreased adherence to therapy, progression of lung disease or comorbidities, and exacerbations of the disease. RRPs conducted for a longer period, under specialized supervision, have a greater chance of changing their way of life.

9. PHYSIOTHERAPY OF ACUTE LUNG PATHOLOGY - POSTURAL DRAINAGE

Postural drainage is a physiotherapeutic method that utilizes body position to maximize the effect of gravity and facilitate the removal of bronchial secretions. The technique requires positioning the patient according to the affected area, so that the bronchi corresponding to each lung segment are vertical; this patient position is associated with thoracic percussion or vibration (tapping vest) facilitating the mobilization of secretions to the main bronchi, from which they will be removed from the lung by coughing.

Drainage is recommended in chronic suppurated bronchitis, bronchiectasis, pulmonary abscess, pulmonary atelectasis by mucosal impact, cystic fibrosis, patients with prolonged artificial ventilation, patients with paralysis or comatose.

Contraindications of percussion or vibration of the thoracic wall are: recent burns or grafting of skin, osteomyelitis, subcutaneous emphysema, tuberculosis, bleeding abnormalities, foreign body intrabronchial, haemoptysis, recent pacemaker insertion, upper abdominal lesions.

Postural drainage prevents pus retention in outbreaks, reduces septic phenomena, facilitates antibiotic action, improves respiration and oxygenation.

Among the risks of drainage techniques are: aggravation of dyspnoea, hypoxia, nausea, vomiting, pain or injury of the chest wall, tachycardia, hypotension, arrhythmias.

The percussion technique is performed with the hand or with a special tapping vest. The hand is held in the form of a cup and the movements are made from the wrist. Drainage is performed before the meal and starts with the most charged areas. Patients with obstructive phenomena may be given bronchodilator treatment 10-15 minutes in advance. There are 2-4 sessions per day, lasting 30-45 minutes. At the end of each drainage position, the patient performs several deep breaths, after which he coughs and expectorates.

Bibliography

1. MURRAY & NADEL'S TEXTBOOK OF RESPIRATORY MEDICINE, SIXTH EDITION. 2016. V.Courtney Broaddus, JD.Ernst, JF.Murray,.
2. Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. AMERICAN THORACIC SOCIETY An Of fi cial American Thoracic Society / European Respiratory Society Policy Statement : Enhancing Implementation , Use , and Delivery of Pulmonary Rehabilitation. 2015;192:1373–86.
3. Spruit MA, Singh SJ, Garvey C, Zuwallack R, Nici L, Rochester C, et al. American Thoracic Society Documents An Official American Thoracic Society / European Respiratory Society Statement : Key Concepts and Advances in Pulmonary Rehabilitation. 2013;188.
4. Cornelison SD. Pulmonary Rehabilitation in t h e Ma n a g e m e n t o f C h ro n i c Lung Disease Pulmonary Rehabilitation Education Training Functioning Self-management. Med Clin NA [Internet]. 2019;103(3):577–84. Available from: https://doi.org/10.1016/j.mcna.2018.12.015
5. Rochester CL, Fairburn C, Crouch RH. Pulmonary Rehabilitation f o r Re s p i r a t o r y D i s o rd e r s Other t han C hronic Ob s t r u c t ive Pulmonary Disease. Clin Chest Med [Internet]. 2014;35(2):369–89. Available from: http://dx.doi.org/10.1016/j.ccm.2014.02.016
6. V.Tudorache. Tratat de reabilitare pulmonară. Ed Mirton, Timişoara. 2009;(ISBN 978-973-52-0574-4).
7. V.Tudorache. Curs de pneumologie. Ed Mirton, Timişoara. 2012.