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RESPIRATORY MEDICINE AND TUBERCULOSIS

SELECTED CHAPTERS

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Respiratory Medicine and Tuberculosis
Selected chapters

Academic textbook

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Index of abbreviations

AAFB	Acid-and alcohol –fast bacilli
ABGs	Arterial blood gases
ABPA	Allergic bronchopulmonary aspergillosis
ACA	Anticentromere autoantibodies
ACE	Angiotensin-converting enzyme
ACO	Asthma- COPD overlap
ACQ	Asthma control questionnaire
ACT	Asthma control test
ACTH	Adrenocorticotropic hormone
ADA	Adenosine deaminase
AE-COPD	Acute exacerbation of COPD
AHI	Apnoeic-hypopnoeic index
AIP	Acute interstitial pneumonia
ALI	Acute lung injury
ALP	Alkaline phosphatase
ANCA	Antineutrophil cytoplasmic antibodies
ARDS	Acute respiratory distress syndrome
ASV	Adaptive servo-ventilation
ATA	Autoantibodies against topoisomerase
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guerin vaccine
BE	Base excess
BiPAP	Bilevel positive airway pressure
BLVR	Bronchoscopy lung volume reduction
BMI	Body mass index
BNP	Brain natriuretic peptide
BOOP	Bronchiolitis obliterans with organising pneumonia
BPAP	Bilevel positive airway pressure
cAMP	Cyclic adenosine monophosphate
CAP	Community-acquired pneumonia
CAT	COPD assessment test
CIH	Chronic intermittent hypoxia

COP	Cryptogenic organizing pneumonia
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease-19
CP	Cor pulmonale
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CSA	Central sleep apnoea
CSR	Cheyne-Stokes respiration
CT	Computed tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
DAD	Diffuse alveolar damage
DIC	Disseminated intravascular coagulation
DIP	Desquamative interstitial pneumonia
DISE	Drug-induced sleep endoscopy
DPLDs	Diffuse parenchymal lung diseases
DRSP	Drug-resistant Streptococcus pneumoniae
EAA	Extrinsic allergic alveolitis
EBUS	Endobronchial ultrasound
ECG	Electrocardiography
ECP	Eosinophilic cation protein
ED	Extensive disease
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EGPA	Eosinophilic granulomatosis with polyangiitis
EMB	Ethambutol
EMG	Electromyography
EOG	Electrooculography
EPAP	Expiratory positive airway pressure
FeNO	Exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
FGF	Fibroblast growth factor
FiO_2	Fraction of inspired oxygen
FVC	Forced vital capacity
G-CSF	Granulocyte-colony stimulating factor
GER	Gastroesophageal reflux

GGO	Ground-glass opacities
GINA	Global initiative for asthma
GOLD	Global initiative for chronic obstructive lung disease
GPA	Granulomatosis with polyangiitis
HAP	Hospital-acquired pneumonia
HCO_3	Bicarbonates (Hydrogencarbonates)
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
ICS	Inhaled corticosteroid
ICSD	International classification of sleep disorders
ICU	Intensive care unit
IgE	Immunoglobulin E
IGRA test	Interferon Gamma Release Assay Test
IIP	Idiopathic interstitial pneumonia
IL	Interleukin
ILDs	Interstitial lung diseases
IFN-γ	Interferon gamma
INH	Isoniazid
IPAP	Inspiratory positive airway pressure
IPF	Idiopathic pulmonary fibrosis
i.v.	Intravenous
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LD	Limited disease
LDH	Lactate dehydrogenase
LIP	Lymphoid interstitial pneumonia
LLN	Lower limit of normal
LTOT	Long-term oxygen therapy
LVRS	Lung volume reduction surgery
MDI	Metered-dose inhaler
MDR-TB	Multidrug-resistant tuberculosis
mMRC	Modified Medical Research Council scale
MPA	Microscopic polyangiitis
MRI	Magnetic resonance imaging
MRSE	Methicillin-Resistant Staphylococcus Epidermidis

MSA	Mixed sleep apnoea
NIV	Non-invasive ventilation
NREM	Non-rapid eye movement sleep
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung carcinoma
NSE	Neuron-specific enolase
NSIP	Nonspecific interstitial pneumonia
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NTM	Nontuberculous mycobacteria
ODI	Oxygen desaturation index
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnoea
OSAS	Obstructive sleep apnoea syndrome
PA	Posteroanterior
$PaCO_2$	Partial pressure of carbon dioxide
PAH	Pulmonary arterial hypertension
PaO_2	Arterial oxygen partial pressure
PAP	Positive airway pressure
PCR	Polymerase chain reaction
PDGF	Platelet-derived growth factor
PEEP	Positive end-expiratory pressure
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PET-CT	Positron emission tomography
P/F ratio	PaO_2/FiO_2 ratio (Horowitz index)
PG	Polygraphy
PH	Pulmonary hypertension
POSA	Positional OSA
PPD	Purified protein derivative
PPFE	Pleuropulmonary fibroelastosis
pro-GRP	Pro-gastrin-releasing peptide
PS	Paraneoplastic syndrome
PSG	Polysomnography
PSI	Pneumonia Severity Index
PZA	Pyrazinamide

RA	Rheumatoid arthritis
RB-ILD	Respiratory bronchiolitis – interstitial lung disease
REM	Rapid eye movement sleep
RIF	Rifampicin
RNA	Ribonucleic acid
RV	Residual volume
RV	Right ventricle
SABA	Short-acting β_2-agonist
SAMA	Short-acting muscarinic antagonist
SCCA	Squamous cell carcinoma antigen
SCLC	Small-cell lung carcinoma
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SITT	Single-inhaler triple therapy
SRBDs	Sleep-related breathing disorders
SSc	Systemic sclerosis (scleroderma)
STM	Streptomycin
TB	Tuberculosis
TGF-β	Transforming growth factor Beta
TGV	Thoracic gas volume
TLCO	Transfer factor for carbon monoxide
TNF-α	Tumour necrosis factor Alpha
TNM system	Tumour - nodus lymphaticus - metastasis classification system.
UIP	Usual interstitial pneumonia
UPPP	Uvulopalatopharyngoplasty
VAP	Ventilator-associated pneumonia
VATS	Video-assisted thoracoscopy
VC	Vital capacity
V_A/Q mismatch	Ventilation-perfusion mismatch
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
XDR-TB	Extensive drug-resistant tuberculosis

1 ASTHMA

Asthma

- Is an airway disease characterised by **chronic inflammation** with increased **airway responsiveness,** which results in airway **obstruction**
- Diagnosis is based on **recurrent respiratory symptoms** (dyspnoea, wheeze, cough, chest tightness) and **lung function tests** (spirometry, bronchodilation test, bronchoprovocation test). **An allergology examination** is required for the detection of asthma **triggers**
- Drugs used for asthma treatment are divided into regularly used long-lasting **controllers** and short-acting **relievers**, used as needed
- The preferred route of administration is by inhalation, with the advantage of high local concentration and lower risk of side effects
- **Inhaled corticosteroids** are currently the most effective among all controllers; the drugs of choice for relieving bronchoconstriction are β_2 mimetics
- **Acute exacerbation** of asthma is signalised by worsening of symptoms, higher variability of lung functions and increased consumption of relievers

DEFINITION AND EPIDEMIOLOGY

Asthma is a heterogeneous disease, usually characterised by **chronic airway inflammation**. It is defined by the **history of respiratory symptoms** such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with **variable expiratory airflow limitation** (based on a consensus statement of Global initiative for asthma-GINA 2021).

Asthma is a common condition, and it is estimated that around 230 -300 million people suffer from this disorder. It is more prevalent in high-income countries, but its prevalence increased greatly over the latter half of the 20th century in both high-income and low-to middle-income countries. It is a common childhood diagnosis but can occur in all ages, with a second peak in people older than 60 years. In adults, it is more prevalent in women and obese people.

AETIOLOGY AND PATHOGENESIS

Aetiology is multifactorial, and the disorder is a consequence of genetic and environmental factors. **Risk factors** for developing the disorder include a family history of asthma, history of atopic conditions (IgE-mediated hypersensitivity like eczema or hay fever),

bronchiolitis in childhood, childhood exposure to tobacco smoke, maternal vitamin D deficiency during pregnancy, and premature birth. Genetic contribution to asthma is complex with genetic heterogeneity. It comprises polymorphisms of the ADAM33 gene and many others.

Triggers of asthma are factors that provoke asthma symptoms in predisposed individuals. They are listed in Table 1.1.

Table 1.1.: **Asthma triggers**

Type of trigger	**Examples**
Allergens	House dust mites, pollen, animal feathers
Airborne irritants	Pollution, tobacco smoke, fumes, cold air, mould
Drugs	Non-steroidal anti-inflammatory drugs (NSAIDs) in "aspirin" asthma, beta-blockers
Infections	Upper respiratory tract infection
Foods	Sulphites and preservatives (wine, food)
Physical activity	Exercise

Exposure to an allergen or another trigger causes the release of inflammatory mediators in the airways. This leads to the activation of inflammatory cells, thus creating a cycle of airway inflammation, including eosinophils, $CD4^+$ T helper (Th) 2 lymphocytes, interleukins, and tumour necrosis factor α (TNF-α), leukotrienes and mast cell tryptase. Neutrophils can also play a role. The inflammation narrows the small airways by increasing mucus secretion, smooth muscle constriction and development of oedema. These changes lead to dyspnoea. The long-term disease can lead to airway remodelling when subepithelial fibrosis prevents the airway from returning to normal diameter. Asthma can be classified as **extrinsic** type (allergic) with known allergen and **intrinsic** when the cause is unknown. The most recent division is into three categories: **allergic asthma**, **eosinophilic non-allergic asthma** (which both are Th2 mediated, called Type-2) and **non-eosinophilic asthma** (non-Type-2).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical features

Patients with asthma have typical respiratory symptoms – **episodic breathlessness** (dyspnoea), **wheeze**, **dry cough,** and a sensation of „**chest tightness** ". The variability of symptoms is usual. Typically, there is a diurnal pattern with symptoms being worse **early in the morning or during the night**. Some patients can be asymptomatic for a longer time, others can suffer only from cough as a predominant symptom, and the lack of wheeze and dyspnoea may signify so-called **cough-variant asthma**.

The sudden onset of all previously mentioned symptoms with dyspnoea as a dominant symptom is called an **asthmatic attack**. An episode with a progressive increase of dyspnoea and other symptoms, and a progressive decrease of lung functions, which represents a significant change from the patient's usual status and requires a change in therapy, is called **asthma exacerbation**. A situation of extreme progression of symptoms with severe dyspnoea not responding to treatment and lasting more than 24 hours is called **severe acute asthma** and can also be named **status asthmaticus**. It manifests with tachypnoea (≥ 25/min), tachycardia, hypotension, inability to speak in sentences, poor chest expansion in inspiration, absence of polyphonic wheeze in auscultation (CAVE! - **silent lung**) and can progress to cyanosis, respiratory failure, and loss of consciousness. Between episodes, there are no signs. In the current disease (while history taking), we ask the patient for triggers of attack (see Table 1.1.).

• **Personal history**. Information about allergy and symptoms of asthma previously (also in childhood) should be obtained.

• **Family history**. Prevalence of asthma is increased in relatives of asthma patients and individuals suffering from eczema, hay fever, and allergic rhinitis.

• **Social history**. Indoor allergens, mostly cat fur, may worsen asthma symptoms. Smoking (including passive smoking) is considered an adverse factor.

• **Occupational history**. Exposure to asthmogenic agents at work can also lead to the development of the disorder. We must ask the patient about current and previous jobs, tasks performed, and materials used.

Investigations

Diagnosing asthma is not often straightforward, and a lot of investigations should be performed between „**suspected asthma**" and the final diagnosis. Many questions must be

answered, a broad spectrum of disorders should be excluded in differential diagnosis, probability of occupational asthma should be taken into account.

Spirometry:

Spirometry is the most important investigation, and diagnosis can be confirmed after demonstration of **airflow obstruction** that responds to treatment (**reversibility**) or changes spontaneously over a short period of time (**variability**). **A reduced forced expiratory volume in one second (FEV_1) and FEV_1/ vital capacity (VC) ratio (called Tiffeneau index) confirms airway obstruction**. The ratio in obstruction is usually under 0.7, but in younger patients also values higher than 0.7 have to be taken into account when FEV_1 and FEV1/VC are below the lower limit of normal (LLN). Some guidelines (or initiatives, e.g., GINA) consider obstructive ventilatory impairment in a ratio of 0.75-0.80 in adult patients and 0.9 in children. However, in some individuals (especially with mild disease), spirometry can be normal between attacks. If airway obstruction is detected by spirometry, the next step is to assess its **reversibility to the bronchodilator** (by inhalation of salbutamol or ipratropium bromide). Positivity of reversibility testing is when FEV_1 improves in 20 minutes by 12% and 200 ml, which supports the diagnosis of asthma. The negativity of reversibility testing does not exclude the diagnosis of asthma, but further investigations must be done. In patients with suspected asthma and normal spirometry, bronchoprovocation tests can be performed to assess bronchial hyperreactivity. Methacholine (or histamine) provocation test is performed using inhalation of nebulised methacholine or histamine, and positivity is defined by worsening of FEV_1 by 20%. For a patient with suspicion of exercise-induced asthma, an exercise provocation test (using bicycle ergometers or treadmill) can be performed.

Variability of spirometry may be observed over several visits to the clinic. Another possibility to prove variability is home **peak expiratory flow rate** (PEFR) measurement when a small, portable device called a peak flow meter is used to measure, and results are recorded in a peak flow diary. A characteristic pattern in asthma is **morning dips**, in which peak flow values are lowest in the morning and improve throughout the day. A 20% variability is highly suggestive of asthma.

Other investigations:

Chest X-ray:

Chest X-ray is usually normal in asthma patients with controlled disease. In an asthma attack, only indirect signs of airway disorder can be present – namely hyperexpanded lungs

(hyperinflation). Chest X-ray is useful in the differential diagnosis (e.g., cardiogenic pulmonary oedema – **CAVE! Asthma cardiale**, pneumothorax, lung cancer, pneumonia) and searching for pathologic states associated with asthma (e.g., ABPA – allergic bronchopulmonary aspergillosis, vasculitis).

Blood tests:

Blood tests comprise a full blood count where eosinophilia can support the diagnosis of eosinophilic asthma. Another useful blood parameter is total immunoglobulin E (IgE), which is elevated in atopy (allergy) and often in allergic (extrinsic) asthma. Furthermore, specific IgE antibodies against particular antigens can be analysed in blood.

Blood gas analysis:

Blood gas analysis is useful in asthma exacerbations (attacks) for the diagnosis of respiratory insufficiency. In clinical manifestations of respiratory insufficiency or transcutaneous oxygen saturation of haemoglobin below 90% (using a pulse oximeter), acute hypoxemic respiratory insufficiency is evidenced by a decrease in arterial oxygen partial pressure (PaO_2) < 8 kPa (or 60 mmHg). The partial pressure of carbon dioxide ($PaCO_2$) is initially lowered (hypocapnia) in hyperventilation; normocapnia in severe hypoxemia is already a warning sign of the developing global respiratory failure (hypercapnic, Type II), which is manifested by hypercapnia, where $PaCO_2 \geq 6$ kPa (45 mmHg). Acidosis can develop (the pH decreases below 7.35), both for metabolic (lactate-producing tissue hypoxia, renal failure) and respiratory (CO_2 retention) causes. In the case of respiratory acidosis, manifested by low pH, hypercapnia, positive base excess (BE) and elevation of bicarbonates (HCO_3), we talk about decompensation of hypercapnic respiratory failure.

Allergy testing (skin-prick tests):

Skin-prick tests may identify atopy and detect sensitivity to a specific allergen. A drop of antigen extract is placed on the surface of the forearm, and the tip of a small stylet is pressed into the superficial epidermis through the drop. A positive reaction manifests with weal and erythema.

Exhaled nitric oxide (NO, FeNO):

Exhaled nitric oxide levels are useful in supporting the diagnosis of asthma and also for treatment management. FeNO is often elevated in allergy and asthma and can decrease as a result of proper inhaled corticosteroid treatment.

Differential diagnosis

Acute or worsened dyspnoea in other diseases must be distinguished from bronchial asthma. Many of the following conditions may also occur in a diagnosed asthma patient, which needs to be distinguished from an asthma attack.

Pulmonary and pleural disorders, in which there is a different physical finding on the chest and the diagnosis is apparent from chest X-ray, are mainly pneumothorax, pneumonia, pleural effusion and atelectasis. A very important point in the differential diagnosis is to consider other disorders associated with airway inflammation and obstructive ventilatory impairment, e.g., chronic obstructive pulmonary disease (COPD), bronchiectasis and cystic fibrosis. A comparison of typical findings in the two most common chronic airway disorders is shown in Table 1.2. Less common episodes of expiratory dyspnoea can occur in pathologic findings in large airways (proximal). These pathologies are too small to be visible on chest X-ray and comprise aspiration of a foreign body and in case of endobronchial tumour (even benign!). Diseases like tracheal stenosis or vocal cord palsy cause mostly inspiratory dyspnoea and are manifested by **inspiratory stridor** (without prolonged expiration) and have to be distinguished from lower airway disorders. In all these findings, the effect of antiasthmatic treatment is weak or completely missing.

Cardiovascular disorders, e.g., **left ventricular heart failure or pulmonary artery embolization,** can manifest with acute dyspnoea. In left ventricular heart failure, the physical finding in auscultation can comprise rales and non-accentual crackles mostly on basal parts of the lung, but sometimes increased vascular filling can cause oedema of bronchial walls and narrowing of airways is manifested with prolonged expiration and expiratory wheezing. This is called **asthma cardiale**. Chest X-ray reveals cardiomegaly and paracardial shadows of lung oedema. Diagnosis can be further supported by laboratory analysis (urea, creatinine, NT-proBNP – N-terminal prohormone of brain natriuretic peptide) and echocardiography. Pulmonary artery embolization can be confirmed by computed tomography angiography (CT-angiography). Chest X-ray findings can be missing but sometimes may reveal several signs, e.g., the disappearance of the vascular drawing in one of the lung lobes (Westermark´s sign).

Table 1.2. Differential diagnosis between asthma and COPD

	ASTHMA	COPD
Onset	Mostly in childhood or in young adults (can be at any age)	Late middle and older age
Smoking	Mostly nonsmokers	Mostly smokers
Cough	Irritable	Mostly productive (sputum)
Exercise-induced dyspnoea	Variable Can be improved by therapy	Dominant sign Progressive despite therapy
Nocturnal symptoms	Common	Rare
Reversibility of obstruction	Common	Small or none
Variability of obstruction	High	Not present
Bronchial hyper-resposibility	Present	Not needed to be tested-bronchial obstruction is present
Allergy testing	Often positive	Often negative
FeNO	Mostly elevated	Normal
Sputum cytology	Eosinophilia	Neutrophilia
Chest X-ray	Normal	Emphysema

ASTHMA CLASSIFICATION

Asthma can be classified from several points of view. Aetiologic division into „extrinsic“ – **allergic** and „intrinsic“ – **non-allergic asthma** cannot be used at the first moment because the aetiology and pathophysiology of asthma are complex. However, basic principles and management are the same in all patients. The most important guidelines were created by GINA, which is regularly updated.

The basic classification is based on the clinical state before the start of treatment. The severity of the disease is evaluated according to:

- Intensity and frequency of daytime and nocturnal symptoms (and frequency of reliever medication usage)
- Intensity and frequency of asthma exacerbations
- Degree of lung function impairment
- Limitation of activities (personal, occupational etc.).

Table 1.3. displays asthma classification according to severity, based on symptoms and lung function test before initiation of treatment.

Intermittent asthma is characterised by the presence of daytime symptoms less than once a week, nocturnal symptoms less than two times a month, exacerbations are mild and short, values of FEV_1 and peak expiratory flow (PEF) are above 80% of reference values and variability of PEF and FEV_1 is less than 20%.

Seasonal asthma (the symptoms are related to the seasonal incidence of allergens – e. g., pollen, and for the rest of a year, they are mild or none) is often incorrectly classified as intermittent asthma. If symptoms are more frequent than is typical for intermittent asthma, it is recommended to classify the disorder as **persistent asthma**.

Table 1.3. Asthma classification according to the severity

Symptoms and lung functions / Asthma type		**Daytime symptoms**	**Nocturnal symptoms**	**FEV_1 and PEF**
Intermittent		rare, mild exacerbations, normal lung functions between episodes	≤ 2-times per month	≥ 80% ref. values variability < 20%
Persistent	**Mild**	> 1-time per week, but not daily, normal lung functions between episodes	> 2-times per month	≥ 80% ref. values variability 20-30%
	Moderate	> 1-time per week	≥ 1-time per week	60-80% ref. values variability > 30%
	Severe	symptoms daily, frequent exacerbations, limitation of physical activities	frequent	≤ 60% ref. values variability > 30%

Mild persistent asthma is manifested by the presence of symptoms more than once per week, but not daily. Exacerbation may influence daytime activity, and sleep quality and nocturnal symptoms are often more than twice a month. Values of FEV_1 and PEF are above 80% of reference values, and the variability of PEF and FEV_1 is between 20-30%.

Moderate persistent asthma – daytime symptoms are common, nocturnal symptoms are more often than once a week, and exacerbation may influence daytime activity and sleep. The patient has an increased need for reliever medication, and lung functions (FEV_1 and PEF) are in the range of 60-80% of reference values. The variability of FEV_1 and PEF is higher than 30%.

Severe persistent asthma is the most severe degree. Daytime symptoms limit physical activity, and acute worsening – exacerbations occur. Values of FEV_1 and PEF are below 60% of reference values, and the variability of FEV_1 and PEF is higher than 30%.

This classification describes the **long-lasting stable state** of the disorder, not the episodes of acute worsening. To qualify for a higher degree of disease severity, only one of the asthma classification criteria is sufficient.

But patients classified in any category can experience a severe, life-threatening asthma attack.

Precise asthma classification is a starting point for proper and effective management of the disorder. The target of treatment and management is to get the disease under control – minimize symptoms and limitation of activity. Therefore, asthma can be classified according to the degree of control – as **well controlled, partly controlled,** and **uncontrolled asthma**. Classification by degree of control is an important part of asthma management and requires evaluation of symptoms using standard questionnaires such as the Asthma control questionnaire (ACQ) and the Asthma control test (ACT).

In some patients, we do not achieve the required level of asthma control even with intensive and long-term treatment. In this case, we can talk about difficult-to-treat (5-17%) and among them even severe asthma (3-4%).

Difficult-to-treat asthma is asthma that is uncontrolled despite 4-5 step treatment (from 5 steps according to GINA guidelines). This group of patients also comprises patients with uncontrolled asthma because of poor inhaler technique, poor adherence to treatment, smoking, comorbidities, or incorrect diagnosis.

Severe asthma is a subset of difficult-to-treat asthma. It is defined as asthma that is uncontrolled despite adequate adherence with maximal optimized therapy and treatment of contributory factors or that worsens when high dose treatment (of inhaled corticosteroids) is decreased.

Less used terms ***brittle asthma*** or ***near-fatal asthma*** are sometimes referred to the cases of difficult-to-treat asthma, in which the course is very variable and unstable, and the patient has recurrent severe seizures and factors predisposing to a poor therapeutic response.

TREATMENT OF ASTHMA

The aim of asthma management is to prevent symptoms and exacerbations- to get the disease **under control**. This management is complex and includes medications and non-pharmacologic approaches.

Drug treatment

Medications used for the treatment of asthma are divided into disease-controlling drugs – „controllers“ (preventers) and symptom-relieving drugs – „relievers“. In adults, there is a possibility to administer therapy in several ways – by inhalation, oral or parenteral administration (subcutaneous, intramuscular, intravenous). The advantage of inhalation is direct therapy in airways which increases the local concentration of drug and minimalizes the risk of systemic adverse effects. Treatment of asthma is stepwise. As the disease worsens, the dose and variety of drugs used to control symptoms are increased. Thus, a mild disease requires step 1 treatment (bronchodilators used intermittently), and severe disease requires step 5 treatment (broad spectrum of anti-inflammatory and bronchodilator medications). The degree of treatment needed to maintain asthma control is also useful for classifying the severity of asthma in the treated patient.

Controllers (preventers) are drugs for maintenance therapy, and they should be used daily. They treat the inflammatory process in asthma and are used alone or in combination with long-acting bronchodilators.

Inhaled corticosteroids (ICS) (e.g., ***beclomethasone dipropionate, budesonide, fluticasone propionate, fluticasone furoate, mometasone, ciclesonide***) are the mainstay of asthma treatment. They reduce airway inflammation, the key underlying process in asthma. They are the most important preventative treatment for persistent asthma in adults. The potency of the various inhaled steroids differs, and the effect of therapy depends on the type of steroid and its dose. The dose of the steroid is increased until symptoms are controlled. Mild persistent asthma needs only low-dose steroid treatment to maintain control, while the severe disease can reach control on a high dose of steroids combined with other drugs. Table 1.4. shows examples of the drugs and doses.

Table 1.4. Daily doses of inhaled corticosteroids for adult patients

Molecule	Low daily dose (μg)	Moderate daily dose (μg)	High daily dose (μg)
Beclomethasone dipropionate	200-500	> 500-1000	> 1000-2000
Budesonide	200-400	> 400-800	> 800-1600
Ciclesonide	80-160	> 160-320	> 320-1280
Fluticasone propionate	100-250	> 250-500	> 500-1000
Fluticasone furoate	100	N/A	200
Mometasone furoate	110-220	> 220-400	> 440

Notes:

- When the disease is already under control, there is a need to titrate the dose of corticosteroid to a **minimal** effect. This is needed to minimalize the risk of adverse effects of steroids.
- **Higher doses are not automatically „more effective" and are associated with a higher risk of adverse effects.** In patients requiring high-dose of inhaled steroids, it is recommended to consider **an** alternative combination of controllers (e.g., ICS- LABA, antileukotrienes, anti-IgE and others)

Long-acting β2-agonists (LABAs) (e.g., ***salmeterol, formoterol, vilanterol***) stimulate β-adrenoreceptors in the smooth muscle of the airway, producing muscle relaxation and thus bronchodilatation. These drugs have a duration of action of more than 12 hours (can be administered twice daily), and some of them (*vilanterol*) more than 24 hours (are used in one dose per day). Drugs with a duration of action of more than 24 hours are also called ultra-LABAs. It is not recommended to use LABA drugs in monotherapy in asthma treatment because they are not anti-inflammatory drugs. However, they have synergic treatment effects with inhaled corticosteroids and therefore, **a fixed combination of ICS -LABA** is the treatment of choice in adults when monotherapy of ISC is not effective in maintaining asthma control. Fixed combination with ICS enables to decrease a dose of inhaled steroid. Typical combinations ISC-LABAs are ***budesonide-formoterol, beclomethasone-formoterol, fluticasone-salmeterol*** or ***fluticasone-vilanterol***. LABAs are drugs with a good safety profile; however, there are some known adverse effects (stimulation of β2-adrenoreceptors affects cardiovascular system – sympatoadrenergic effect), and they include tachycardia and palpitations (e.g., in formoterol use), tremor and hypokalaemia (increasing risk of arrhythmias).

Long-acting muscarinic antagonists (**LAMAs**) act as bronchodilators by inhibiting the broncho constrictive effect of the vagus nerve on bronchial smooth muscle. From this group of drugs (more used in the treatment of chronic obstructive pulmonary disease – COPD), ***tiotropium bromide*** is commonly used in asthma. It is used as an additional bronchodilator drug in severe asthma in steps 4-5 of stepwise treatment. At present, the new LAMA molecule ***glycopyrronium***, which is known for the treatment of chronic obstructive pulmonary disease, is also entering the treatment of asthma. It is part of ICS / LABA / LAMA combinations,

containing all three basic components of inhalation therapy. This treatment is called SITT-single-inhaler triple therapy and combinations currently used are ***beclomethasone/ formoterol/ glycopyrronium*** and ***mometasone/ indacaterol/ glycopyrronium***.

Leukotriene antagonists (e.g., ***montelukast, zafirlukast***) are acting by blocking the effects of cysteinyl leukotrienes (molecules with bronchoconstrictor and proinflammatory actions). Leukotriene antagonists are administered orally in tablet form. They can be used as a controller in monotherapy in children, but in adults, they are used as add-on therapy (added to ICS-LABA).

Systemic corticosteroids (oral, parenteral) are mostly used for the treatment of asthma exacerbations. They are sometimes used in the long term for patients with very severe asthma not controlled by high doses of inhaled steroids alone. However, this treatment is limited by significant adverse effects, including osteoporosis, hypertension, iatrogenic Cushing syndrome (facies lunata, central obesity, hirsutism), diabetes mellitus, suppression of hypothalamic–pituitary–adrenal axis, cataract, glaucoma, skin atrophy and striae, myopathy, gastroduodenal ulcer, and psychic disorders. Long-term administration of oral steroids induces immunosuppression and increases the risk of infections (tuberculosis, herpes zoster). Therefore, not oral corticosteroids but inhaled are the gold standard for the treatment of asthma.

Methylxanthines (theophyllines) are nonspecific inhibitors of phosphodiesterase and increase cyclic adenosine monophosphate (cAMP) stimulation of β-adrenoreceptors. Their additional bronchodilation effect is not great, and they are administered orally as add-on therapy to ICS-LABA. Their place in asthma management is limited, as their blood levels should be monitored. Low doses have a small synergic anti-inflammatory effect with steroids, but high plasma levels are toxic. Adverse effects in high doses include cardiac arrhythmias, cramps, diarrhoea and gastro-oesophageal reflux. ***Aminophylline*** (intravenous theophylline) is also available, but it is not used as a controller and is currently also no more recommended in the management of asthma exacerbation.

Sodium cromoglycate was once a common drug used as a controller. It has a very limited anti-inflammatory effect and is less effective than a low dose of inhaled steroid. It was a nonsteroid preventative but currently is no more recommended in guidelines.

Monoclonal antibodies (also called biologic therapies) are novel drugs acting against particular targets associated with allergic or eosinophilic inflammation. ***Omalizumab*** (anti-IgE)

is a monoclonal antibody (a type of protein) that binds to immunoglobulin E. It is a parenteral drug (subcutaneous administration) prescribed to patients with severe allergic (IgE-mediated) asthma who are not controlled by high-dose ICS and LABA. Other drugs – ***mepolizumab*** and ***reslizumab*** (anti-interleukin-5/ IL-5) are monoclonal antibodies acting against eosinophils. Indication for treatment is non-allergic eosinophilic asthma not controlled by high-dose ICS and LABA. IL-5 stimulates the growth and activity of eosinophils. By attaching to IL-5 and blocking its activity, the antibodies reduce the number of eosinophils in the blood and lungs. ***Benralizumab***, which does not bind to IL-5 alone but to IL-5 receptor on the eosinophil surface, has a similar treatment effect. ***Dupilumab*** is a monoclonal antibody designed to block receptors (targets) for IL-4 and IL-13, which are also involved in the immune cascade. By blocking these receptors, dupilumab prevents IL-4 and IL-13 from working and relieves disease symptoms.

Antihistamines are drugs indicated for treatments of asthma with significant allergy and allergic comorbidities (allergic rhinitis). A potential mild adverse effect of these drugs is sedation, which is of lower prevalence in modern H_1- antihistamines. In patients with **atopy** (allergy), the use of specific immunotherapy (vaccination) can decrease symptoms associated with particular allergens.

Relievers (relieving medications) – are drugs used to relieve symptoms. They are used on-demand, and they can reverse bronchoconstriction.

Short-acting β_2-agonists (SABAs) – (e.g., ***salbutamol/ albuterol, fenoterol, terbutaline***) have the same mechanism of action as LABAs. They have an immediate effect (within 15 minutes) but also a limited duration of action (4-6 hours). They are drugs of a first choice in relieving symptoms, mostly in asthma exacerbations and for preventing exercise induces asthma symptoms. This relieving medication should be prescribed to every patient; however, they are not suitable for regular use and for maintaining asthma control (use only on demand). Increased consumption more than two times per week (not as prevention of exercise-induced asthma) is a warning signal of low asthma control. Common adverse effects are tremor and tachycardia; therefore, it is not recommended to use more than eight puffs per day (even in exacerbation). Patients consuming more than 10-12 puffs per day have an increased risk of fatal asthma.

Short-acting muscarinic antagonists (**SAMAs**) produce bronchodilatation by blocking the bronchoconstrictor effect of vagal nerve stimulation of the bronchial smooth muscle. The available compound is ipratropium bromide, which is a less effective reliever than

SABA, but without adverse effects of β_2-agonists. The maximal bronchodilation effect can be achieved with a combination of SABA/SAMA in one inhaler**.**

Magnesium sulphate – administered as an intravenous infusion (1.2-2 g in 20 minutes), is a smooth-muscle relaxant. It is safe a may be useful in acute severe asthma as an additional drug to nebulised SABAs and systemic corticosteroids.

MANAGEMENT AND PREVENTION OF ASTHMA

Effective asthma control can be achieved using pharmacotherapy and non-pharmacologic approach.

Control of the disease is defined as:

• no daytime symptoms
• no night-time wakening due to asthma
• no need for reliever medication
• no exacerbations
• no limitation of physical activity
• normal lung function (FEV_1 and PEF > 80% predicted)

Non-pharmacological approaches in asthma management include:

• smoking cessation – smoking does not primarily cause asthma, but smoking (including passive smoking) significantly decreases asthma control and increases the risk of exacerbation (and risk of smoking-related disorders).
• weight loss – mostly in obesity-related asthma (which is mostly not responding to inhaled corticosteroids – corticoresistance, in comparison to allergic asthma, which is corticodependant)
• breathing exercises, sports are recommended – hiking, nordic walking, swimming
• allergen reduction or removal (e.g., stopping exposure to occupational allergens, home allergens – dog, cat, cleaning home environment – vacuum cleaning, using anti-allergic bed sheets)
• psychologic support

Self-management of asthma – is a term used for an approach when a patient under the support of a physician is able to recognize asthma symptoms and, according to the warning signs of decreased asthma control (e.g., PEF variability), is able to modify the dose of inhaled steroids

or use oral steroids (prescribed for emergency use). The patient is educated about the diagnosis and its symptoms, treatment (reason for the use of controllers and relievers) and use of different inhalers. There is a need to create a partnership between the patient and his/her physician. Patients should start their treatment at the step most appropriate to the initial severity of their asthma, and treatment is adjusted consecutively. Treatment should be „stepped-up“ as much as necessary to control asthma. And when the control has been achieved, treatment may be later (not earlier than three months) „stepped-down “so that patient is on treatment than is necessary. Inhaler with reliever drug should be prescribed to every patient as a rescue medication. A very important condition in asthma control is the patient's adherence to pharmacotherapy. When a patient with good asthma control (achieved by medication) stops using the inhaled medication, there is an increased risk of losing control, and asthma exacerbation can develop. Patients should be aware of factors which can lead to asthma exacerbations. Some **drugs** (e.g., *acetylsalicylic acid* – Aspirin or NSAIDs) may cause severe exacerbations and patients with a case history of such reactions should avoid using them. Beta-blockers may cause bronchoconstriction, and patients with asthma can use only cardioselective beta-blockers (under careful monitoring of adverse effects). **Emotional stress** may potentially lead to asthma exacerbation by the mechanism of hyperventilation (and hypocapnia) induced bronchoconstriction. **Allergic rhinitis and polyposis** are frequent comorbidities of asthma, and they need to be treated (while there is the same type of inflammation in the upper airways). **Gastroesophageal reflux** is a disease that can trigger asthma attacks, mostly in childhood and asthma control can improve when it is successfully treated. And asthma control can change (get worse or better) during **menstruation** and **pregnancy.**

ACUTE SEVERE ASTHMA

The sudden onset of all previously mentioned symptoms with dyspnoea as a dominant symptom is called an **asthmatic attack**. An episode with a progressive increase of dyspnoea and other symptoms, and a progressive decrease of lung functions which represents a significant change from the patient's usual status and requires a change in therapy, is called **asthma exacerbation**. A situation of extreme progression of symptoms with severe dyspnoea not responding to treatment and lasting more than 24 hours is called **acute severe asthma**, which can be named **status asthmaticus**. It manifests with tachypnoea (≥ 25/min), tachycardia, hypotension, inability to speak in sentences, poor chest expansion in inspiration, absence of polyphonic wheeze in auscultation (CAVE! – **silent lung**) and can progress to cyanosis,

respiratory failure, and loss of consciousness. Between episodes, there are no signs. In the current disease, we ask the patient for triggers of attack (see Table 1.1.).

Severity assessment and treatment

Assessment of the severity of asthma exacerbation is a key to proper treatment. Treatment can be managed in the office or by hospitalisation in the general ward or in the intensive care unit (ICU). Primary care for exacerbation consists of repetitive inhalations of short-acting bronchodilators, early administration of systemic corticosteroids and oxygen supplementation. Breathing frequency, pulse rate, oxygen saturation and blood gasses of the patient are carefully monitored. The aim of treatment is to relieve the airway obstruction, reverse the hypoxemia and prevent relapse of the disorder. The patient should also be closely monitored after discharge from ICU to determine whether his asthma control improves.

In case of **mild-moderate exacerbation**, the most effective way to reverse the bronchial obstruction is to administer SABA (2-4 puffs every 20 minutes in the first hour). After the first hour, the dose of SABA depends on exacerbation severity. Administration of systemic (oral) corticosteroids as a rescue medication is recommended.

Severe exacerbations (acute severe asthma) require close monitoring in the workplace of intensive care (ICU or anaesthesiologic department). Patients suffering from a severe asthma exacerbation are often unable to speak in sentences and give a history. Obtaining essential components of history is useful and includes:

• the duration of asthma and level of asthma control
• current treatment
• information about previous attacks (frequency, severity, hospitalisations)
• any recent exposure to triggers (e.g., upper respiratory tract infection, exposure to pollen, animals)

Physical examination focuses on the assessment of severity, ability to speak, heart and breath rate and accessory respiratory muscle use (and paradoxical thoraco-abdominal breathing). Chest X-ray is needed for exclusion of complications and other diagnoses (e.g., pneumonia, atelectasis, pneumothorax). We always investigate oxygen saturation in arterial blood, and if the patient's condition permits, there is an option to perform a functional examination (PEF, FEV_1) optimally before starting treatment. PaO_2 values during arterial blood tests below 8 kPa (60 mmHg) indicate the presence of hypoxaemic respiratory failure. The key to the severity of the condition is the evaluation of $PaCO_2$. Patients with mild to moderate exacerbation of asthma usually have low $PaCO_2$. It is because their tachypnoea blows off carbon

dioxide. But hypoxemia (in a dyspnoeic patient with paradoxical breathing) associated with normal or high levels of $PaCO_2$ (above 6 kPa / 45 mmHg) is a major cause for concern. Hypercapnic respiratory failure (with respiratory acidosis) increases the risk of treatment failure and the need for intubation mechanical ventilation.

Table 1.5. summarizes clinical findings in severe and life-threatening asthma.

Table 1.5. Clinical assessment of asthma severity

Asthma severity	**Clinical findings** (any from the list)
Severe asthma	Respiratory rate ≥ 25/min
	Heart rate ≥ 110/min
	Inability to complete sentences in one breath
	PEF < 50% of predicted
Life-threatening asthma	Silent chest, cyanosis, or poor respiratory effort
	Bradycardia or hypotension
	Exhaustion, confusion or loss of consciousness
	O_2 saturation < 92% or PaO_2 < 8 kPa
	Normal or high $PaCO_2$
	PEF < 33% of predicted

The following medications are usually given concomitantly in order to end exacerbation as quickly as possible. **Oxygen** is administered via a nasal cannula or mask until saturation is 90-94%. We must be cautious when administering oxygen to patients with normal or high $PaCO_2$! In patients with severe airway obstruction, $PaCO_2$ may severely increase when oxygen saturation approaches 100%! Nebulised **β_2-agonists (SABAs)** are administered as first-line treatment immediately and regularly, mostly 2-4 puffs of ***salbutamol*** or ***fenoterol*** every 15-20 minutes in the first hour. After the first hour, the dose of SABA depends on exacerbation severity. In certain cases, beta-agonists may also be administered parenterally. When a rapid therapeutic response is required, ***terbutaline*** can be administered by any of the three standard parenteral routes: subcutaneous, intramuscular, or intravenous (i.v.). bolus (0.25-0.5 mg). The preferred routes will usually be subcutaneous or intramuscular. Rescue administration of **systemic corticosteroids** is obligatory. The maximum effect of systemic corticosteroids in acutely aggravated asthma occurs after 4-6 hours. Oral treatment (prednisone 40-50 mg daily

dose) is preferred, which is as effective as intravenous hydrocortisone 100 mg intravenously (every 6-12 hours). 5-day treatment is effective and should not exceed seven days in the prevention of adrenal suppression. The combination of nebulized SABA with an anticholinergic (***ipratropium bromide***) may provide better bronchodilation than each of the above drugs alone. Intravenous ***magnesium sulfate*** is not used for routine treatment of asthma exacerbations but may help in some patients who have not responded to the initial treatment. Subcutaneous or intramuscular administration of ***adrenaline*** is not routinely indicated during asthma exacerbations but is indicated (and is a treatment of choice) for acute anaphylaxis and allergic angioedema, which can be a cause of acute severe asthma exacerbation. Intravenous **theophylline** (***aminophylline***) is currently not recommended in the management of asthma exacerbation.

2 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD)

- Is chronic progressive **inflammatory airway and lung disorder** associated with partially reversible **bronchial obstruction, destruction of lung parenchyma** and systemic consequences
- Diagnosis is based on a history of **exposure to noxious inhaled particles or gases** (mostly smoking), symptoms of **progressive exercise-induced dyspnoea** and **cough** and **lung function test examination** (spirometry, bronchodilation test, body plethysmography)
- Treatment interventions include **smoking cessation**, **pharmacotherapy** (with the preference for **inhaled medications**), **physiotherapy**, and in case of respiratory failure, also long-term **oxygen** treatment. **Lung transplantation** can be considered.
- Inhaled medications include bronchodilators (short and long-acting) **β_2-agonists** and **muscarine antagonists.** They can be combined together or with anti-inflammatory-acting **corticosteroids**. **Theophylline** can be administered orally as well as selective phosphodiesterase inhibitor – **roflumilast**
- **Acute exacerbation** of COPD is defined as an **acute worsening of respiratory symptoms** (dyspnoea, increased sputum production, sputum purulence) that results in **additional therapy.** Exacerbations are treated with a short course of systemic corticosteroids, an increase of bronchodilation therapy, and antibiotics (in case of sputum purulence). Severe exacerbations require oxygen treatment and sometimes also non-invasive ventilation

DEFINITION AND EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

COPD is a leading cause of morbidity and mortality. Its prevalence increases and is between 4-10% (5% in Slovakia). It is estimated that 400-600 million people worldwide suffer from COPD, and globally, there are 3 million deaths annually.

AETIOLOGY AND PATHOGENESIS

Risk factors for the development of COPD can be divided into factors of environment (exogenic) and genetic predisposition (endogenic). Smoking (tobacco, marihuana) is the most common risk factor for COPD. It accounts for most COPD cases in high-income countries. Exposition to tobacco can be in smokers (active or ex- smokers) quantified using pack-years. Smoking history is obtained, and one pack-year is defined as the equivalent of one pack (20 cigarettes) per day for one year.

$$1 \text{ pack-year} = 1 \frac{\text{year of smoking } \mathbf{x} \text{ 20 cigarettes}}{20}$$

However, passive exposure to cigarette smoke is also a significant risk factor, but it cannot be quantified. Exposure to smoke from solid fuel used for cooking is a major cause of COPD in low-income countries. COPD may be further aggravated by air pollution, but its role in the development of COPD is unclear.

Individual responsiveness to noxious particles and gases is determined mostly by **genetic predisposition**. Many factors in early childhood have an important influence on the development of the lung by determining the maximum lung function achieved in adolescence. The genetic factors contributing to the susceptibility to developing COPD are poorly defined, and genes associated with metabolic and inflammatory pathways are potentially involved. However, the aetiology of COPD is multifactorial, and many genes can be involved in pathogenesis. There is only one known cause of genetic disorder associated with COPD in 1-2% of COPD patients. It is a genetic deficiency of the principal antiprotease, **α_1-antitrypsin**, which is associated with the development of severe emphysema at a young age. There are some other endogenic risk factors of COPD, which are impaired lung development, repetitive airway infections, low socio-economic status, and gender (females are more susceptible to developing COPD).

Exposure to toxic particles causes an excessive **chronic inflammation** of the airways driven by macrophages, CD8 T-lymphocytes and neutrophils. They produce an increased number of cytokines, especially interleukin-8, TNF-α and leukotriene B4. Together with an increased inflammatory process, an **imbalance of proteinase and antiprotease** develops in the lungs. It comprises an increase in proteinase production and reduction of antiproteases (e.g., in α_1-antitrypsin deficiency), allowing the proteinases to digest lung tissue. Furthermore,

oxidative stress also has a significant effect on the reduction of antiprotease activity. As a result of these effects, three main features of COPD develop. These are small airway obstruction **(obstructive bronchiolitis), mucus hypersecretion** and destruction of lung parenchyma (**emphysema**). The proportion of these features is different in individual patients and affects clinical manifestation. Airway obstruction can be detected as a limitation of airflow in lung function testing (**obstructive ventilatory impairment** – see Chapter 1 Asthma). Obstructive ventilatory impairment is a **mainstay of COPD diagnosis**. It is because COPD is defined by obstruction and not by the presence of chronic bronchitis or emphysema. **Chronic bronchitis** is defined clinically as a productive cough (expectoration of sputum) that lasts for three months or more per year for at least two consecutive years. It can be a separate diagnosis and can also be a phenotype of COPD. **Emphysema** is defined in terms of its pathological features that consist of dilatation of the lung distal to the terminal bronchiole with the destruction of their walls. It is a consequence of inflammatory processes and proteases, but also of mechanical influences – namely, by a mechanism of **air trapping**. The peripheral airflow limitation progressively traps gas during expiration, resulting in **hyperinflation** (an increase of residual volume). Destruction of alveoli by emphysema leads to loss of elastic recoil and loss of outward traction on the small airways, leaving them prone to collapse on expiration. Two main patterns of emphysema are recognised: centriacinar (centrilobular) and panacinar (panlobular). Panacinar emphysema is a characteristic feature of patients with α_1-antitrypsin deficiency. However, the presence of emphysema (e.g., on a CT scan) does not define COPD as it can be a diagnosis on its own and also can be associated with other diagnoses (e.g., asthma).

Gas exchange abnormalities in progressive disorder results in hypoxaemia and hypercapnia. Hypoxaemia in COPD is a consequence of many factors – airway obstruction, alveoli destruction, pulmonary hypertension, and ventilation-perfusion (V_A/Q) mismatch. Hypercapnia is a result of reduced ventilation (hypoventilation) and may be due to impaired ventilatory drive or increased dead space ventilation. The abnormalities in alveolar ventilation and a reduced pulmonary vascular bed further worsen the V_A/Q (ventilation-perfusion ratio) abnormalities. Hypoxaemia is a stimulus for **hypoxic pulmonary vasoconstriction** and the development of **pulmonary hypertension**, which is often manifested by chronic right heart failure – **cor pulmonale chronicum**.

Clinically stable COPD can be worsened by **acute exacerbations**. They lead to intensified symptoms, worsened quality of life, drastically deteriorated lung functions and increased risk of death. The factors causing exacerbations include mainly respiratory tract

infections (bacterial, viral), air pollution, cold and dry weather, smog, or noncompliance with the treatment.

Systemic consequences and extrapulmonary features of COPD are probably associated with so-called systemic inflammation, in which increased numbers of inflammatory cells and increased concentrations of inflammatory mediators such as C-reactive protein (CRP) are in circulating blood. The direct consequence is weight loss (**cachexia**) and skeletal muscle dysfunction. The mechanism of systemic inflammation is also likely to contribute to the frequent occurrence of **comorbidities** in patients with COPD, such as cardiovascular disease, osteoporosis, anaemia, metabolic syndrome and diabetes, depression and cognitive disorders, and lung cancer.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical features

The clinical development of COPD is often hidden, and in many patients, the disease is only recognized at an advanced stage. The characteristic clinical manifestation (sometimes it is the only symptom) of the airway obstruction and emphysema is **breathlessness**, initially during exertion. Some patients have a sedentary lifestyle, which masks symptomatology in earlier stages of the disorder. In the late stages, dyspnoea is present with minimal exertion associated with conducting basic day-to-day activities. Airway disorder can also be manifested by other symptoms, like chest tightness and wheezing or cough.

Intolerance of physical exertion does not have to be conditioned only by ventilating limitations; it can also be influenced by cachexia and skeletal muscle dysfunction or manifestation of right-ventricular heart failure.

Chronic cough and sputum production are a manifestation of chronic inflammation in the airways and mucus hypersecretion. Chronic bronchitis is defined as a productive cough that lasts for three months or more per year for at least two consecutive years.

Acute exacerbation of COPD is defined as an acute worsening of respiratory symptoms (dyspnoea, increased sputum production, sputum purulence) that results in additional therapy. Worsening of symptoms is beyond daily variability, and new symptoms may occur temporarily (fever, nasal hypersecretion, swelling of ankles and calves).

Physical examination of a patient with a mild degree of COPD severity may not detect any deviations from the norm during the symptom-free period. In more advanced stages, we can observe dyspnoea, involvement of accessory respiratory muscles, prolonged expiration, and cyanosis. In some patients, weight loss to cachexia. In others, weight gain due to swelling in right ventricular failure. When examining the chest, we can notice the barrel-shaped thorax in advanced emphysema associated with hyper-resonant (hypersonic) percussion. In pulmonary auscultation, a noticeably prolonged expiration with diffuse bronchial side-phenomena, like wheezing and rhonchi, is typically present. Vesicular breathing may be diffusely attenuated by dominant emphysema, sometimes as the only auscultation sign of acute exacerbation, and can be associated with **paradoxical breathing** (diaphragmatic paradox). This pathological respiratory pattern is in COPD patients manifested by retraction of the abdominal wall during inhalation. Subcostal and substernal retractions are often visible, but also supraclavicular retractions can occur. Paradoxical breathing is a sign of severe disorder and inability to ventilate.

Several **clinical patterns (phenotypes)** of COPD can be discerned. Historically, two major (classical) phenotypes of COPD have been described – **pink puffer** (with emphysema) and **blue bloater** (as a description of a patient with chronic bronchitis). The phenotype of pink puffer characterizes a patient with dominant emphysema (hyperinflation), typically with a barrel-shaped chest, severe dyspnoea in exertion, accessory muscle activity and pursed-lipped breathing. Patients often have muscle wasting and low body mass index (BMI). The blue bloater phenotype is mostly described simply for a patient with chronic bronchitis. As chronic bronchitis is defined only by cough, this phenotype is more complex. It can be defined as the presence of chronic bronchitis, less hyperinflation, cyanosis, obesity, peripheral oedema, metabolic and cardiovascular comorbidities, and a high risk of sleep-disordered breathing (mostly sleep apnoea). Currently, these classical terms are not often used, but in case of distinct and noticeable traits of disease, patients can be classified in phenotypes- bronchitis, emphysema, asthma- COPD overlap (ACO), and phenotypes with bronchiectasis, cachexia, and frequent exacerbations.

Investigations

Spirometry

Spirometry is more precisely described in the previous chapter (Chapter 1 – Asthma). Spirometry and the procedure of the forced manoeuvre is the **crucial method for diagnosis of the disease**. According to the definition, the diagnosis is confirmed by spirometry results showing **irreversible** (persistent) **airflow obstruction** (obstructive ventilatory impairment). Reducing the FEV1 / FVC ratio **below 0.7** is a diagnostic criterion for the presence of bronchial obstruction, fulfilling the definition of COPD. This ratio is generally taken to define airway obstruction irrespective of age. Once airway obstruction has been determined to be present (by a ratio below 0.7), its **severity is classified by comparing FEV_1 to the predicted value**. The COPD severity (according to obstruction) is arbitrarily divided into degrees: mild, moderate, severe, and very severe (see Table 2.1). In the spirometry examination to confirm the diagnosis of COPD, it is necessary to consider the post-bronchodilator values of these parameters (i.e., the highest achievable values that should always be in the zone of bronchial obstruction, unlike bronchial asthma). The test itself is negative in many COPD patients (i.e., there is little or no bronchodilation), but this is not a prerequisite - in a minority of patients, there is a more pronounced bronchodilator response (COPD with a feature of bronchial hyperreactivity or asthma-COPD overlap).

Body-plethysmography examination (a method of functional examination of the lungs, allowing the assessment of the entire volume of air in the chest by means of changes in pressure in a hermetically sealed cabin) may objectify a permanent increase in **residual volume (RV)** (and thoracic gas volume – TGV) in the lungs – confirming **pulmonary hyperinflation** (in emphysema). Functional examination of the lungs is necessary at the time of diagnosis of the disease and repeatedly at each re-evaluation of the condition (e.g., after exacerbation or change of treatment). Values of functional parameters (in a patient already treated with bronchodilator therapy, the values are considered post-bronchodilator) tend to progressively deteriorate over time in COPD.

Oximetry (pulse oximetry) is useful in measuring **oxygen saturation non-invasively,** and it is widely used for screening and monitoring respiratory failure. In suspicion of respiratory insufficiency, a sample of **arterial blood** is necessary to assess PO_2 and $PaCO_2$ levels, pH and HCO_3^- to determine whether the patient has type 1 or type 2 respiratory failure.

Other investigations:

Chest X-ray: Posteroanterior and lateral chest X-ray is always performed at baseline pneumological examination as well as when new or worsening existing respiratory symptoms occur. It is not necessary to confirm the diagnosis of COPD, but it displays hyperinflation of the chest, with flattened, low hemidiaphragms, a long narrow cardiac shadow and increased retrosternal airspace on the lateral film. In addition, it shows signs of pulmonary hypertension (enlarged pulmonary arteries, bulging of the right ventricle). The chest X-ray is also an important investigation in **excluding additional diagnoses** (e.g., lung cancer, pleural effusion, lung oedema) and in **detecting complications** of COPD (e.g., pneumothorax, pneumonia).

High-resolution CT scans can demonstrate the extent of emphysema (and its distribution-panacinar, centriacinar) and the presence of emphysematous bullae or bronchiectasis.

Bacteriological examination of sputum is beneficial for **targeted treatment of infectious exacerbation** of COPD, serological examination for the presence of antibodies against atypical pathogens, or virological examination helps to detect infections with microorganisms possibly contributing to manifestations of exacerbation (*Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, respiratory viruses).

Blood tests: Blood tests comprise full blood count where blood eosinophil count with a threshold ≥ 300 cells/μL can predict the effectivity of inhaled steroids in reduction of COPD exacerbations.

Blood gas analysis:

Blood gas analysis is useful in COPD exacerbations but also in the stable disease for assessment of respiratory insufficiency. See Chapter 1 – Asthma.

Differential diagnosis of diseases with the presence of bronchial obstruction is given in Chapter 1 – Asthma.

COPD CLASSIFICATION

Classification of COPD is based on a combined assessment of the degree of severity of bronchial obstruction, the severity of symptoms, and the frequency of exacerbations. Depending on the severity of the bronchial obstruction, COPD is classified into four stages

according to GOLD (Global initiative for chronic obstructive lung disease): 1 – mild, 2 – moderate, 3 – severe and 4 – very severe (Table 2.1).

In assessing the intensity of the symptoms, we can concentrate either on one prominent symptom (i.e. dyspnoea) or on a panel of several symptoms. Breathlessness can be quantified using the **modified Medical Research Council scale (mMRC)**, with five grades:

• Grade 0 – breathless only on strenuous exercise

• Grade 1- breathless when hurrying on the level or walking up a slight hill

• Grade 2 – more breathless than contemporaries when walking on level ground

• Grade 3 – breathless on walking about 100 m

• Grade 4 – breathless on dressing or undressing

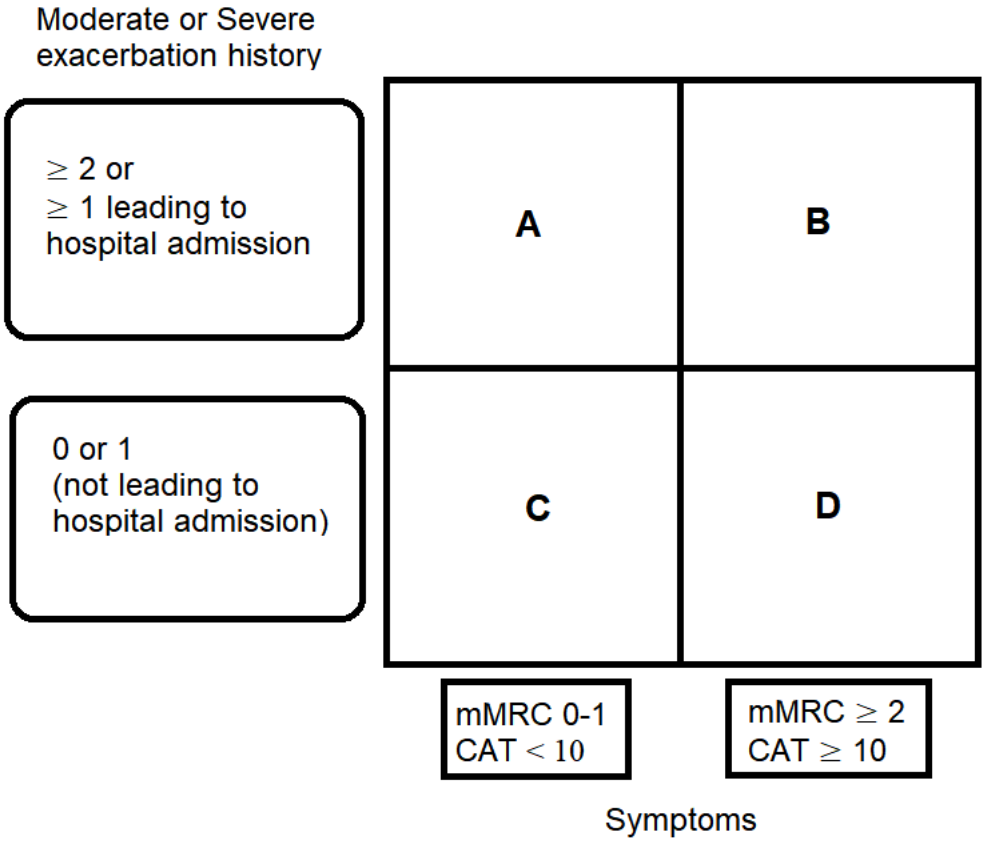
Other questionnaires are available for assessment of other symptoms, overall function, quality of life and impact of the disease (e.g., COPD assessment test – CAT).

Symptom intensity is displayed on the horizontal axis of the classification scheme – low left, high right (Table 2.2). The vertical axis of the classification scheme shows the level of risk (exacerbations and mortality) of COPD patients related to the prevalence of exacerbations in the previous year (0-1 – low risk, 2 or more – high risk). Considering all of these areas, we classify a COPD patient into one of the four stages of the disease (A – low risk, low symptoms, B – low risk, multiple symptoms, C – high risk, low symptoms, D – high risk, multiple symptoms) and to one of four degrees of severity of the bronchial obstruction (indicated by the Arabic numerals 1 to 4). According to this scheme (GOLD), the subject is classified by number and letter (e.g., GOLD 2 B, or GOLD 4 D).

Table 2.1. Classification of airflow limitation severity in COPD

Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1)	
GOLD 1. Mild	$FEV_1/FVC < 0,7$ $FEV_1 \geq 80\%$ predicted
GOLD 2. Moderate	$FEV_1/FVC < 0,7$ $50\% \leq FEV_1 < 80\%$ predicted
GOLD 3. Severe	$FEV_1/FVC < 0,7$ $30\% \leq FEV_1 < 50\%$ predicted
GOLD 4. Very severe	$FEV_1/FVC < 0,7$ $FEV_1 < 30\%$ predicted

Table 2.2. COPD classification, based on a combined assessment of symptoms and risk of exacerbations



MANAGEMENT OF COPD

Smoking cessation

It is strongly recommended for every COPD patient to stop smoking. It is the most effective way to reduce symptoms and preserve/slow down the rate of lung function decline. Smoking cessation is the **strongest disease modifier** (slowing the rate of lung function decline). All patients still smoking, regardless of age, should be encouraged to stop and offered help to do so at every opportunity. The recommendation for first contact intervention is summarized in the five principles, called "5A", listed in Tab. 2.3.

Table 2.3. „5A "– simple first contact smoking cessation intervention

Intervention	Aim
1. Ask	To identify if the patient continues to smoke
2. Advise	Take a clear position on the harmfulness of smoking
3. Assess	Assess the patient's motivation to stop and willingness to cooperate
4. Assist	Support the patient's decision using available procedures
5. Arrange	Continue monitoring, plan additional controls

About 5% of smokers can stop smoking at their own discretion without any assistance. Using the available interventions, a much higher percentage of smokers can successfully get rid of their habit. Only about one-fifth of them will succeed for the first time, so it is necessary to intervene repeatedly. Specialized centres combine **psychotherapy** (e.g., cognitive-behavioural techniques) and **pharmacotherapy**. **Nicotine replacement therapy** approximately doubles the rate of success of attempts at smoking cessation. It is available as transdermal patches, chewing gums, and oral or nasal sprays. It is a safe method but not recommended in pregnancy. **Varenicline** is a nicotinic receptor portal agonist. It reduces cravings for and decreases the pleasurable effects of cigarettes, and through these mechanisms, it can assist some patients in quitting smoking. **Electronic cigarettes** and **tobacco heating systems** are currently not recommended for smoking cessation, as there is no evidence of smaller harmfulness and can potentially increase the addiction.

Pharmacotherapy of stable COPD

In COPD treatment, similar drug groups are used as in asthma (see Chapter 1 – Asthma) but are not divided into controllers and relievers. Inhaled bronchodilation therapies are the mainstay of the treatment of COPD. An application of an aerosol ("spray," e.g., MDI – metered-

dose inhaler) or powder form (DPI – dry powder inhaler) of the drug directly into the airways is used. Bronchodilator drugs and inhaled glucocorticosteroids, which utilize their anti-inflammatory action, are present in inhalation form.

Long-acting bronchodilators include long-acting muscarine antagonists (**LAMAs**) and long-acting β_2-agonists (**LABAs**), and they represent the first step in treatment. Mechanisms of action are described in Chapter 1 – Asthma. In the LAMA group, ***tiotropium, glycopyrronium*** and ***umeclidinium*** are widely used. Their duration of action is at least 24 hours. ***Aclidinium bromide*** has a shorter duration of action and needs to be delivered twice daily. In the LABA group, ***indacaterol***, ***vilanterol*** and ***olodaterol*** (acting 24 hours) and ***formoterol*** (with duration of action at least 12 hours) are used. These drugs offer a prolonged relief of symptoms and improve lung functions and exercise tolerance. The mechanism is bronchodilation and consecutive reduction of hyperinflation. Hyperinflation is the main mechanism of dyspnoea in COPD patients. In symptomatic patients, it is recommended to use the combination therapy – ***dual bronchodilator (LAMA/LABA)***. The combination of drugs is beneficial for patients with persistent symptoms and progression of obstruction and has better outcomes (for symptoms, lung functions and exacerbation frequency) than a single bronchodilator.

Corticosteroids have a different place in treatment strategy in comparison to asthma. In asthma, inhaled steroids are the first step in controlling the disease, and long-action bronchodilators are an add-on therapy. In COPD, the inhaled corticosteroid has a beneficial effect on the reduction of exacerbations and hospital admissions. This effect is greatest when inhaled corticosteroid is combined with a LABA in a combination inhaler. Typical combinations are ***budesonide-formoterol, beclomethasone-formoterol, fluticasone-salmeterol*** and ***fluticasone-vilanterol***. The most recent drugs are the so-called **triple therapies**, which contain LABA, LAMA and ICS in one inhaler. Available combinations for COPD are ***beclomethasone-formoterol-glycopyrronium*** and ***fluticasone-umeclidinium-vilanterol***. Inhaled corticosteroids and combinations with ICS are appropriate and effective in patients with frequent exacerbations and elevated blood eosinophil count ≥300 cells/μL peripheral blood.

Short-acting bronchodilators – are used and recommended only as a rescue medication to reduce acute symptoms and in the treatment of COPD exacerbation.

Methylxanthines – mostly oral ***theophylline*** is an add-on therapy to inhaled medications. These drugs may help control symptoms of dyspnoea and wheeze. They

have significant adverse effects, mostly cardiovascular (arrhythmogenic effects). Plasma levels need to be monitored – as the therapeutic window is narrow. The dose should be reduced if a macrolide or fluoroquinolone antibiotic is prescribed.

PDE-4 inhibitor – *roflumilast* is a selective inhibitor of phosphodiesterase 4 and is used as an oral medication. It has some benefits in reducing exacerbation frequency in patients with severe COPD with chronic bronchitis phenotype. It should not be used in combination with methylxanthines because of a risk of multiplication of effects (because theophyllines are nonspecific phosphodiesterase inhibitors).

Mucolytics (e.g. ***acetylcysteine, erdosteine***) are drugs increasing the expectoration of sputum by reducing its viscosity. They can also reduce the frequency of exacerbation s of COPD in patients who have a chronic productive cough. They should be used with caution, especially in patients with weak respiratory muscle strength. In these patients, on the other hand, it may increase the amount of mucus in the airways.

Other treatment possibilities for COPD

The physical activity of patients is limited at all stages of COPD, and its reduction is associated with higher morbidity and mortality of the patients, regardless of the degree of lung function impairment.

Vaccination

Influenza vaccination is recommended for all patients with COPD. Pneumococcal vaccinations are recommended for patients > 65 years of age and also for younger patients with comorbidities like chronic heart disease. Recently, a vaccine against COVID-19 is also suitable for patients with COPD.

Pulmonary rehabilitation is a multidisciplinary programme for COPD patients which is focused on the reduction of dyspnoea, improvement of exercise tolerance and quality of life. Rehabilitation is a complex programme containing **exercise training, smoking cessation, education, breathing control techniques, social and psychological support and nutrition**.

Treatment of respiratory failure depends on its type. Chronic **hypoxemic respiratory failure** (Type 1) can be treated with oxygen. ***Long-term oxygen therapy*** is offered to a patient with $PaO_2 < 7.3$ kPa. In patients with PaO_2 in the range of 7.3 – 8.0 kPa, it is prescribed when they meet additional criteria (e.g. low FEV_1, presence of pulmonary hypertension). Long-term oxygen therapy can improve the prognosis (and extend life) of hypoxic COPD patients by preventing hypoxia-induced pulmonary hypertension (**cor pulmonale**). In the case of chronic **hypoxemic-hypercapnic respiratory failure** (type 2), domiciliary ***non-invasive ventilation*** is recommended.

Treatment of comorbidities (listed in paragraph aetiology and pathogenesis) is very important in the complex management of every single COPD patient because **comorbidities and systemic consequences of COPD significantly affect patients' morbidity and mortality**. All health care specialists in COPD management need to work together with professionals specialized in the management of other major chronic diseases to provide a multidisciplinary treatment strategy for COPD patients with comorbidities.

Surgery is an option for patients suffering from emphysema. ***Bullectomy*** may be appropriate if a large bulla is compressing the viable surrounding lung. ***Lung volume reduction surgery (LVRS)*** is aimed at resecting functionally useless areas of the lung, thereby reducing the overall volume. ***Bronchoscopy lung volume reduction (BLVR)*** is an emerging alternative to surgery with the same aim. These treatments include valve, coil, thermal vapour ablation, bio-lung volume reduction, targeted lung denervation, and airway bypass stent.

Lung transplantation is an option for those patients with a very advanced stage of COPD with respiratory failure. However, comorbidities in COPD patients, as well as a lack of donor organs, severely limit the utilisation of this procedure.

Management of acute exacerbations of COPD

Acute exacerbation of COPD (AE-COPD) is defined as an acute worsening of respiratory symptoms (dyspnoea, increased sputum production, sputum purulence) that results in additional therapy. They may occur spontaneously in case of chronic treatment interruption or because of infection. Cold weather also provokes these worsenings. In terms of severity, they can be classified into 3 degrees of severity. **Mild AE-COPD** can be managed at home by

increasing the dose and frequency of a short-acting bronchodilator (SABA and/or SAMA). **Moderate AE-COPD** require a course of ***oral prednisolone*** and/or ***antibiotic***. **Severe AE-COPD** require ***admission to the hospital*** or ***a visit to the emergency room***.

We administer ***short-acting inhaled bronchodilators*** (nebulised or using metered-dose inhaler – MDI), both from the group of β2-sympathomimetics (SABAs) and muscarine antagonists (SAMAs). The standard dose is one puff (of MDI inhaler) every hour for 2-3 doses and then every 2 to 4 hours based on the patient's response. Administration of ***methylxanthines*** (oral or parenteral) is no more recommended in the management of AE-COPD.

A very important treatment in AE-COPD is a ***course of corticosteroids***. Standardly, an oral ***prednisolone*** 30 mg/daily for 5-7 days is administered (alternatively, *methylprednisolone* or intravenous *hydrocortisone* 100-200 mg/daily). Antibiotics should be administered if findings suggestive of bacterial aetiology of infectious exacerbation (sputum purulence, increased laboratory markers of bacterial inflammation) are present. Usually, we use them empirically, but as soon as possible, adjust the treatment according to the results of sputum cultures. Correction of water and electrolyte balance is essential, as well as ensuring nutrition and preventing thromboembolism. In case of **hypoxaemic respiratory failure, *controlled oxygen therapy*** is required. Oxygen is administered via a nasal cannula, but in case of mouth breathing (often in AE-COPD), a simple oxygen mask or special Venturi mask is needed. The target oxygen saturation is **88-92%** to prevent oxygen-induced hypoventilation and hypercapnia (in patients with an increased risk of Type 2 respiratory failure). Patients with established hypercapnic (type 2) respiratory failure do not respond to CO_2 stimulus to ventilation properly, and their respiration is driven by hypoxaemia. If they are given high concentrations of oxygen, they lose the drive to breathe, and hypoventilation results in increased hypercapnia, acidosis, narcosis, respiratory depression and, ultimately, death. Occasionally, a **decompensation of hypercapnic respiratory failure** (manifested with respiratory acidosis) complicates an AE-COPD. N***on-invasive ventilation (NIV)*** using bi-level positive airway pressure (BPAP) should be employed in case of a decrease in pH below the normal range (< 7.35). When used properly, NIV not only reduces the likelihood that patients will progress to need invasive ventilation but is demonstrated to reduce inpatient mortality. In case of failure of NIV, ***invasive mechanical ventilation*** should be considered.

3 PNEUMONIA AND PLEURAL EFFUSION

Pneumonia

- Is an **acute inflammation** in the area of respiratory bronchioles, alveolar structures and pulmonary interstitium, most often caused by an **infectious pathogen.** The infection can follow **aspiration** or **inhalation** of various substances
- The predominant symptoms are **cough**, mostly productive, **fever**, **dyspnoea**, **pleuritic chest pain,** and haemoptysis may be present in some patients. Typical auscultation finding on the lungs are **coarse crackles** (crepitations) above the site of inflammatory infiltration, and **bronchial breathing** in lobar pneumonia
- The diagnosis is confirmed by **chest X-ray** (new consolidations in the lung parenchyma, corresponding to symptoms and objective findings); **microbiological examinations** are needed to identify the causative pathogen
- The basis of treatment is **anti-infective chemotherapy** (empirical **combined antibiotic treatment** of community-acquired pneumonia and, according to the results of microbiological examinations, subsequently targeted antibiotic, antiviral, antifungal or antiparasitic treatment), supplemented by **symptomatic treatment** (antipyretics, mucolytics, rehydration, oxygen
- **Pleural effusion** is defined as the presence of an excessive amount of fluid in the pleural cavity, etiologically in various conditions (inflammation, tumour, systemic causes). It must be diagnosed by **pleural puncture** with the examination of the punctate (biochemical, cytological, culture); the treatment depends on the underlying disease

DEFINITION AND CLASSIFICATIONS

Pneumonia is an acute inflammatory process in the respiratory bronchioles, alveolar structures and pulmonary interstitium. The cause of pneumonia is most often an infectious pathogen, but it can also be an infection following aspiration into the lower respiratory tract, inhalation of gaseous substances or aerosols, or reaction to radiation or toxin. Entry of infection into the lung parenchyma is possible by inhalation, aspiration or haematogenous dissemination from another infection site. The severity of pneumonia and the tendency to adverse complications are modified by several risk factors such as age, cardiovascular and respiratory comorbidities (chronic heart failure, chronic obstructive pulmonary disease, lung cancer), smoking and immunodeficiency conditions (haematological malignancies, therapy with

corticosteroids, diabetes mellitus, alcohol abuse and others). According to the World Health Organization (WHO), pneumonia is the third most common cause of death. Mortality is higher in children under four years of age and then rises again with age over 60 years.

From an etiopathogenetic point of view, pneumonia is a heterogeneous disease. **According to the causative infectious pathogen**, pneumonia can be divided into ***viral, bacterial, fungal,*** and ***parasitic***. However, the fact that up to approximately 50% of pneumonia fails to determine the etiological agent must be considered when deciding on a therapeutic approach. Pneumonia can be further divided **according to the time course** into ***acute, recurrent*** (at one or different sites) and ***chronic*** with the development of carnification of the pulmonary parenchyma, or according to pathological-anatomical findings for ***lobar*** pneumonia, ***lobular*** (so-called ***bronchopneumonia***) and ***interstitial pneumonia*** (often viral). It is currently not recommended to use the division into ***typical*** and ***atypical pneumonia***, as the causal relationship between the causative pathogen and the clinical picture of pneumonia has not been confirmed. It is very important to assess the **severity of pneumonia** (more details in the treatment chapter).

From a **clinical-epidemiological point of view**, the division into ***community-acquired pneumonia*** and ***nosocomial pneumonia*** is most used.

Community-acquired pneumonia (CAP) is common pneumonia acquired in the community outside a hospital facility. This group of pneumonia is the most common (up to 90% of cases). **Hospital-acquired pneumonia (HAP)** is acquired in a hospital setting and is developing at least 48 hours after admission, and its manifestation, which, due to its incubation time, can be expected for another 14 days after the patient is discharged from the medical facility. A particularly risky group are patients treated with mechanical ventilation, usually in intensive care units with the occurrence of resistant nosocomial pathogens, where we speak of the so-called **ventilator-associated pneumonia (VAP)**. Each type is characterized by a spectrum of predominant pathogens and thus a rational choice of empirical anti-infective treatment.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical features.

The sudden onset of symptoms of an acute respiratory infection is characteristic. The most common symptom is **cough**, which may be unproductive at first, later often becoming productive. Sputum is often purulent, sometimes with minor haemoptysis. Fever and sweating are common. In the beginning, there are shaking chills. In large pneumonia or in people with comorbidities with reduced functional reserve, **dyspnoea** occurs. **Pleural pain** in the chest occurs when the pleura is affected by an inflammatory process. **Extrapulmonary symptoms** include headache, arthralgia, myalgia, dyspepsia, hepatic, renal or myocardial involvement, splenomegaly, etc. An eruption of herpes labialis is common.

Physical examination objectifies febrility usually above 38ºC, tachypnoea, facies pneumonica (febrile face with cyanosis of the lips and puffy mouth with rapid breathing). In auscultation of the lungs, respiration is usually alveolar with audible secondary respiratory phenomena, typically coarse crackles (rales) – this finding corresponds to the pathomorphological picture of bronchopneumonia. In lobar pneumonia with the consolidation of the alveoli of the entire lung lobe, no side effects are heard (air does not enter the alveoli), pathological tracheal (tubular) breathing is present, and localized dull percussion can be detected. **Crepitations** (inspiratory) may be present with predominant interstitial involvement and in early (crepitus indux) and late (crepitus redux) stages of pneumonia. Sometimes the auscultation finding is poor and inconspicuous, even despite extensive inflammatory infiltrates.

The most common **complications of pneumonia** are pleuritis, and parapneumonic pleural effusion, which may be further complicated by the development of thoracic empyema, pulmonary abscess, and lung gangrene (characteristic with *foetor ex ore*). Extensive or complicated pneumonia can result in **acute respiratory insufficiency**. General complications of pneumonia include sepsis and septic shock, renal failure, and myocardial infarction.

Imaging and laboratory examinations.

All patients with community-acquired pneumonia should have a **chest X-ray** performed in posteroanterior (PA) projection to verify the diagnosis as well as to detect complications (pleural effusion, lung abscess, multilobe involvement). The diagnosis is based

on **the presence of a lower respiratory tract infection** and a **newly discovered finding of an infiltrate on a chest X-ray**. The decision on hospitalization or outpatient treatment depends on the experience and judgment of the physician, and although there are no strict criteria for it, there are recommendations for hospitalization based on the severity of the condition (see Chapter – Treatment). In addition to the severity of pneumonia, the physician must consider the presence of comorbidities and risk factors, as well as non-medical motives (social background, patient's wishes).

In hospitalized patients, routine haematological and biochemical screening, blood gas and acid-base balance tests and basic urine (chemical) and urinary sediment examinations are usually performed. In the above examinations, we usually find **laboratory signs of inflammation** (increased sedimentation of erythrocytes, CRP, procalcitonin). In the blood count analysis, leucocytosis with neutrophilia and an increased incidence of young, immature white blood cells, mostly non-segmented forms of polymorphonuclear cells (shift to the left), is common. In severe pneumonia, **hypoxaemic respiratory failure**, pH changes, retention of nitrogen metabolites (urea, creatinine), electrolyte abnormalities, osmolality, glycemia, and others may be found.

Several **microbiological and serological screening methods** are available to detect the causative pathogen. Culture examination of sputum is simple but coughed sputum is often contaminated with the bacterial flora of the oropharynx, so a representative sample can be obtained in only 20-30% of cases. If the patient does not cough up, it is possible to use assisted expectoration methods (administration of expectorants, induction of cough by inhalation of saline solution). Sputum can be examined microscopically, stained with Gram stain and also Ziehl-Neelsen staining, which is suitable for the detection of acid-and alcohol-fast bacilli (AAFB). There is also a need to cultivate the sputum to detect *Mycobacterium tuberculosis*. Serological methods are used to examine serum IgM and IgG antibody titres against mycoplasma and chlamydial antigens and against respiratory viruses. The dynamics of the titres of the monitored antibodies are monitored by repeated sampling with an interval of 14 - 21 days. Furthermore, an antigen of *Legionella pneumophilla* can be detected in urine in severe infection. Severe course of pneumonia or lack of response to initial treatment are reasons for intensified efforts for etiological diagnosis using invasive procedures. In such cases, bronchoalveolar lavage at **bronchoscopy**, pleural puncture at effusion, and rarely biopsy of lung tissue is important to obtain material to determine the cause of pneumonia. In case of presumed bacteraemia or septic conditions, blood collection for culture (blood culture) is indicated.

TREATMENT

In all patients with pneumonia, **initial empirical antimicrobial therapy** should be initiated immediately, with a spectrum of action covering the most prevalent pathogens, considering individual risk factors. CAP is caused by *Streptococcus pneumoniae* and a group of so-called atypical pathogens, bacteria without a cell wall, characterized by intracellular parasitism (mycoplasma, chlamydophila, legionella). Only in some cases will it be possible to identify the causative agent and subsequently implement targeted antibiotic treatment according to sensitivity. In addition, at the time of setting up pneumonia treatment, it is necessary to decide on the possibility of outpatient treatment at home, or on the need for hospitalization, in a standard ward or intensive care unit. These options roughly correspond to the division of the clinical course of pneumonia into mild, moderate, and severe. There are several scoring systems and scales to determine the severity of the clinical course of pneumonia and the so-called **risk stratification**. The more complex PSI (Pneumonia Severity Index) scale used in the United States considers age, gender, a variety of co-morbidities, and clinical and laboratory findings. It has a very high predictive value, but its wider use in practice limits the relatively time required for proper evaluation. An example of a simplified evaluation scheme is the **CURB-65 scale** (table 3.1). It allows a quick assessment of the condition, but as it only evaluates certain parameters, it may not be completely accurate. Clinical judgement, social circumstances and the stability of the comorbidities are also very important in assessing disease severity.

Table 3.1. CURB-65 severity score

CURB-65 score	Assessment
• **C**onfusion • **U**rea >7mmol/L • **R**espiratory rate ≥30/min • **B**lood pressure (Sys. <90mmHg or Dia.<60mmHg) • **A**ge ≥ 65 years Score 1 point for each feature present	**0-1 points**: outpatient treatment **2 points**: consider hospitalisation **3 or more points**: severe pneumonia – in-patient treatment **4-5 points**: admission to ICU

Pneumococcal pneumonia

The most proven pathogen in community-acquired pneumonia is *Streptococcus pneumoniae* (referred to as pneumococcus). It is thought to be responsible for most pneumonia without evidence of an etiological agent. Unlike pyogenic streptococcus (the cause of tonsilitis), pneumococcus is, in most cases, resistant to penicillin. Therefore, broad-spectrum **aminopenicillins (*ampicillin, amoxicillin*)** are used in treatment in high doses, or better **aminopenicillins protected by beta-lactamase inhibitors** (***ampicillin-sulbactam, amoxicillin-clavulanate***), also possibly **III. generation cephalosporins** (***ceftriaxone, cefotaxime***). Equally effective alternatives are the representatives of the new generation of so-called **antipneumococcal (respiratory) fluoroquinolones** (***levofloxacin, moxifloxacin***), the effect of which is enhanced by the ability to achieve higher concentrations at the site of action (alveolar fluid, macrophages) than their plasma concentrations. It is important from a therapeutic point of view that pneumococcal strains with a high degree of resistance to basic penicillin antibiotics are also resistant to lower-generation cephalosporins, macrolides, doxycycline and co-trimoxazole. These strains are collectively referred to as *Drug-resistant Streptococcus pneumoniae* (DRSP). Many of them are also resistant to first-order fluoroquinolones, represented by ciprofloxacin. However, DRSPs are still sensitive to the above-mentioned recommended groups of antibiotics. The glycopeptide ***vancomycin*** and the newly developed oxazolidinone ***linezolid*** serve as reserve antibiotics. However, it is often not necessary to resort to reserve antibiotics, even for pneumococcal bacteraemia and sepsis. Reserve antibiotics remain reserved for the treatment of pneumococcal meningitis. Risk factors that increase the likelihood that pneumonia is caused by DRSP are age over 65 years, antibiotic treatment of any infection in the previous three months, immunodeficiency conditions, and multiple comorbidities.

Pneumonia caused by „atypical pathogens “

The term "atypical pneumonia" has traditionally been used to describe pneumonia in which the **uncharacteristic course of the disease** (often present non-productive cough, sub febrility and non-respiratory symptoms - headache, arthralgia, myalgia) and an **inconspicuous physical finding** in the lungs does not correspond to **extensive lung disease**. The division into **typical and atypical pneumonia is currently not recommended**, as the clinical course of

pneumonia does not clearly indicate its causative agent, and even coinfection with typical and atypical pathogens is possible. The so-called **atypical pathogens** involved in the pathogenesis of pneumonia are mostly intracellular parasites (*Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophilla*, rarely *Coxiella burnetii*) or respiratory viruses. **The initial empirical treatment of each of any community-acquired pneumonia must be effective against both typical and atypical pathogens**, regardless of the current clinical course. Pneumonia caused by atypical pathogens may also have a severe per acute course with the possible development of serious complications (including acute respiratory distress syndrome – ARDS). Infections with atypical pathogens often occur in groups of young people (dormitories, military units), where their epidemics can also occur. The proportion of pneumonia caused by atypical pathogens is estimated at about 40% of all pneumonia cases.

In the treatment of pneumonia caused by atypical pathogens, the administration of antibiotics that penetrate intracellularly and interfere with the proteosynthesis of microorganisms is recommended. This group of antibiotics includes:

1. macrolides (basic ***erythromycin***, more modern ***spiramycin*** and currently the most widely used ***clarithromycin*** with advantageous pharmacokinetics and significantly better tolerability, and the azalide derivative ***azithromycin***),

2. tetracyclines (***doxycycline*** is the most widely used in clinical practice), and

3. fluoroquinolones (the older generation is ***ofloxacin, pefloxacin, norfloxacin***, ***ciprofloxacin***, the newer generation includes the already mentioned ***respiratory fluoroquinolones***, which are also effective for pneumococci).

Pseudomonas pneumonia

In deciding whether to use antimicrobial therapy, special consideration should be given to whether pneumonia is caused (even with co-infection) by *Pseudomonas aeruginosa*. Risk factors for pseudomonas infection are mainly structural changes in the airways and lungs (bronchiectasis, cystic fibrosis), systemic glucocorticoid therapy, broad-spectrum antibiotic therapy during the last month and malnutrition. If reasonably suspected, treatment regimens contain some of the **antipseudomonal beta-lactam antibiotics** - ***ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam***, which are also excellently effective against pneumococci. In case of beta-lactam allergy, the monobactam antibiotic ***aztreonam*** may alternatively be administered. Treatment with any of these beta-lactam antibiotics is always

combined with another class of antibiotics with antipseudomonal activity; usually, the **aminoglycoside antibiotic *gentamicin*** or the antipseudomonal **fluoroquinolone *ciprofloxacin*** is added.

Community-acquired pneumonia treatment strategy

Pneumonia in low-risk patients. In patients without a history of high-risk comorbidities who have not used antibiotics in the last three months, the first-line treatment regimen is to target pneumococci without presumed antibiotic resistance and atypical pathogens **monotherapy** with a modern **macrolide** such as ***clarithromycin*** or ***azithromycin***. Only if a macrolide is contraindicated (allergy), the ***doxycycline*** is the second-line drug, with a higher risk of resistance in pneumococci.

Pneumonia in patients at high risk or severe course. We mean the risk for the presence *of DRSP-type pneumococcus* with the need for an adequately effective treatment regimen (macrolide resistance is presumed), which also has a good clinical effect on other relatively common respiratory pathogens such as *Klebsiella pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and others. Equivalent first-line alternatives in uncomplicated patients at risk are a **combination of an antipneumococcal beta-lactam antibiotic and a macrolide** or **antipneumococcal fluoroquinolone monotherapy**. If previous use of antibiotics is a risk factor for pneumococcal resistance, we select a substance that has not yet been administered. At the same time, we prefer parenteral administration, with the possibility of switching to the oral form after the first 3-5 days of administration. In case of unavailability or intolerance of the macrolide, a **combination of an antipneumococcal beta-lactam antibiotic** and ***doxycycline***, which has the disadvantage of photosensitization, is permissible.

Severe course pneumonia with a risk of pseudomonas infection. A combination therapy containing an **antipseudomonal beta-lactam antibiotic** and **fluoroquinolone**, possibly with an **aminoglycoside** (***gentamycin***), is used. When administering ***gentamicin*** to critical patients, its nephrotoxicity must be considered. The recommended treatment regimens also effectively cover DRSP-type pneumococci and the spectrum of atypical pathogens.

Pneumonia caused by rare pathogens

When detecting an etiological agent and determining susceptibility, antimicrobial treatment is corrected according to the results of laboratory tests. In case the initial empirical treatment fails, and we can detect **penicillin-resistant staphylococci**, the use of an **antistaphylococcal antibiotic** (***methicillin, oxacillin***) is appropriate and in case of infection with **methicillin-resistant *Staphylococcus epidermidis* (MRSE)** strain in risk groups (persons from social care facilities, etc.) **glycopeptide antibiotic** – ***vancomycin*** or ***teicoplanin***. Similarly, for other proven pathogens, appropriate specific treatment should be used unless included in the empirically used initial monotherapy or combination. In case of clinical suspicion of **anaerobic infection**, or if proven, combination therapy includes ***metronidazole*** or the **lincosamide antibiotic *clindamycin***, as well as in the development of a pulmonary abscess.

Pneumocystis jirovecii (formerly known as *carinii*) pneumonia is common in patients with HIV (human immunodeficiency virus) infection. It is diagnosed cytologically by evidence of parasite cysts in bronchoalveolar lavage. Specific treatment is ***pentamidine***, also available in aerosol form. ***Co-trimoxazole*** (***trimethoprim-sulfamethoxazole***) is also effective.

The causative agents of *fungal* pneumonia can be diagnosed by culture examination for mycoses or by visualization of fungal components in a biopsy sample. Some fungal infections, especially in immunocompromised patients with haematological malignancies, have a characteristic picture on computed tomography (CT) lung examination, which in this case is sufficient for diagnosis. Systemic **antifungal therapy** (***amphotericin B, voriconazole, caspofungin***) is required.

In *viral* pneumonia, older preparations of ***amantadine*** and ***rimantadine***, which are effective against the influenza A virus, are available for antiviral therapy. The newer **neuraminidase inhibitors *zanamivir*** and ***oseltamivir*** are effective in H1N1 influenza A virus infection. In case of proven herpetic infection, administration of ***acyclovir*** is indicated, and *cytomegalovirus* infection in immunocompromised patients (e.g., after organ transplants) is treated with ***ganciclovir***. During the *Coronavirus*-induced COVID-19 pandemic, the antiviral drug ***remdesivir*** was conditionally approved for the treatment of severe pneumonia in patients in 2020. However, specific therapy is not known against the most common causes of viral respiratory infections, such as *Rhinovirus*, *respiratory syncytial virus* (RS-virus) and *Adenovirus*.

Mycobacterium tuberculosis (Tuberculosis pneumonia, so-called Acute Pneumonic Phthisis) can also be the cause of the disease, which initially occurs acutely in the form of lobar

pneumonia. Long-term administration of **antituberculotic** drugs is necessary in case of an established TB infection.

Hospital-acquired pneumonia

HAP is the second most common infection threatening hospitalized patients in a hospital setting and the most common infection acquired in ICU. In most cases, they occur in patients with **invasive mechanical ventilation** (***ventilator-associated pneumonia***). In terms of prognosis, we divide it into **early** (within five days of connecting to the ventilator) and **late infection**. In the first days after intubation and the onset of mechanical ventilation, a debilitated patient usually develops pneumonia caused by community-acquired airway flora – *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*. Late infection in a ventilated patient has a significantly worse prognosis, mostly typical hospital polyresistant strains of *Pseudomonas aeruginosa, Acinetobacter calcoaceticus, Serratia marcescens, Proteus mirabilis* and fungi. Gram-negative enteric bacteria (*Escherichia Coli* etc.) predominate as etiological agents in non-ventilated patients, often associated with lower airway aspiration.

Recommendations for the treatment of nosocomial pneumonia emphasize, in the first place, the knowledge of local conditions about the epidemiology and resistance of microorganisms. In principle, however, especially in ventilated patients, we do not hesitate with invasive diagnostic procedures (obtaining bronchoalveolar aspirate by bronchoscopy, blood culture). Empirical and subsequent targeted antimicrobial treatment is **combined** and applied **parenterally**. Intravenous **cephalosporins III and IV. generation**, parenteral **aminopenicillin protected by a beta-lactamase inhibitor** (***ampicillin-sulbactam***), **antipneumococcal fluoroquinolones** or ***clindamycin*** and ***aztreonam*** are suitable for early hospital-acquired pneumonia. In late-onset pneumonia, parenteral **antipseudomonal beta-lactams** (***piperacillin-tazobactam***) or **carbapenems** (***imipenem-cilastatin, meropenem***) or ***ceftazidime*** are administered together with ***ciprofloxacin***, or **aminoglycoside** (***gentamycin, amikacin***). In legionella-induced nosocomial pneumonia, a parenteral **macrolide** (***azithromycin*** or ***clarithromycin***) is administered; in case of epidemiological data on methicillin-resistant staphylococci, **glycopeptides** (***vancomycin, teicoplanin***), alternatively ***linezolid*** or ***synercid***.

Depending on the clinical condition and microbiological findings, we also consider the application of systemic **antifungals** (***amphotericin B, voriconazole***).

Pneumonia in immunocompromised patients

Pneumonia in immunocompromised patients can be caused by unusual pathogens as well as by the same pathogens that cause CAP. Symptomatology depends on the pathogen and on the conditions compromising the immune system. In patients, a history of **congenital or acquired immunodeficiency** and **laboratory examination** of leukocyte counts, cellular immunity and immunoglobulins are important. **The emphasis in diagnostics is placed on blood culture and bronchoscopy samples, but serology can also be useful.** Treatment depends on the immune system defect and the pathogen. In organ or bone marrow transplantation recipients with bilateral interstitial pneumonia, the *cytomegalovirus* may be the cause, or the disease is idiopathic. A pleural-based consolidation may be caused by *Aspergillus fumigatus* infection. In patients with acquired immunodeficiency syndrome (AIDS), bilateral pneumonia is usually *P. jirovecii* pneumonia. Treatment consists of broad-spectrum empirical antibiotic therapy and consultation with an infectious diseases specialist (microbiologist). Based on the presumed infection or the identified agent, targeted treatment with antifungals (e.g. ***amphotericin B, voriconazole***) is started for fungal infections, and virostatics for viral diseases (e.g. ***acyclovir, ganciclovir***). ***Co-trimoxazole*** is used for the treatment of *Pneumocystis jirovecii*. Furthermore, specific therapy to enhance immune system function can be administered based on immunologist consultation. For example, patients with chemotherapy-induced neutropenia may receive ***granulocyte-colony stimulating factor*** (G-CSF), and patients with hypogammaglobulinemia due to an inherited or acquired disease (e.g., leukaemia) should receive ***intravenous immune globulin***.

Symptomatic and supportive treatment of pneumonia. The treatment of pneumonia is based on anti-infective treatment, but the dominant clinical manifestations can be influenced by symptomatic treatment. We alleviate fever with antipyretics; mucolytics are suitable for difficult expectoration, and less often, we use antitussives for irritating coughs. However, administration of **mucolytics** (***ambroxol, N-acetylcysteine***) is not appropriate in immobile non-cooperating patients, as an increase in mucus production may lead to worsening of the condition. Pleurodynia can be controlled by short-term administration of analgesics. In indicated cases, regulated oxygen therapy and possibly bronchodilators are applied. In severe pneumonia, complicated by the development of acute respiratory insufficiency, transient respiratory support or mechanical ventilation is required in indicated cases. Adequate hydration and correction of disorders of blood counts of electrolytes and acid-base balance is a matter of course. In severe pneumonia requiring intensive care, prevention of thromboembolism by

fractionated heparin, antisecretory treatment with proton pump inhibitors such as prevention of gastroduodenal stress ulcer and consistent maintenance of euglycemia are required.

Prevention of pneumonia in adulthood

Pneumococcal vaccines, polysaccharide or conjugated, contain a mixture of purified capsular polysaccharide antigens of the most common serotypes of Streptococcus pneumoniae, which are responsible for 85-90% of invasive pneumococcal infections. It is beneficial in all people over the age of 65, as well as in younger people in the presence of chronic diseases (heart failure, COPD, diabetes mellitus, alcoholism, liver cirrhosis, asplenia) or risk circumstances (long-term stay in social care institutions). The gradually decreasing antibody response lasts for 5-10 years after vaccination. Revaccination is possible in a person vaccinated before the age of 65 years after more than five years from the first administration of the vaccine. Persons vaccinated for the first time over the age of 65 will not be revaccinated.

Influenza vaccine in the form of purified inactivated virus, its fragments (subvirions) or surface antigens. Every year, the expected modification of the prevailing serotypes for the following season is prepared. The influenza A virus H3N2 and H1N1 surface antigen chains and the influenza B virus chain are updated. It is, therefore, necessary to vaccinate each year before the period of the highest incidence of the disease, always with a newly updated vaccine. The effectiveness of the vaccine depends on the match of the circulating virus chains in the population and the vaccine chains, and with a good match, it is 70-90%. In the elderly, the effectiveness in preventing the disease is lower, but even the developed flu has a lighter course after vaccination and does not affect the lower respiratory tract, which reduces the incidence of serious complications (pneumonia) and mortality. In view of this, it is important to vaccinate people over the age of 65, as well as patients with chronic diseases and groups of people at increased risk of transmitting influenza (health professionals, workers in school groups and social care facilities).

COVID-19 vaccine is a vaccine intended to provide acquired immunity against COVID-19 (Coronavirus disease 19) caused by the SARS-COV-2 virus. In 2020, a national regulatory authority approved different vaccines for public use: ribonucleic acid (RNA) vaccines (Pfizer–BioNTech and Moderna), conventional inactivated vaccines (Sinopharm and

Sinovac), and viral vector vaccines (Gamaleya Research Institute and AstraZeneca). There is a difference in dosing in vaccines; some of them should be administered in 2 doses. In the Pfizer vaccine, the interval is 21 days between the first and second dose (booster). For the Moderna COVID-19 vaccine, the interval is 28 days between the first and second dose. In 2021, a single-dose Johnson&Johnson/Janssen vaccine was introduced. In addition, another protein vaccine Nuvaxovid from Novavax was expected to be approved in 2022.

PLEURAL EFFUSION

Pleural effusion is a fluid accumulation within the pleural space. The physiological amount of pleural fluid in an adult is 10 - 20 ml, and normally, there is a balance between the constant formation of fluid and its resorption. Accumulation generally occurs when its formation exceeds resorption. According to the protein content in pleural effusion, which depends on the pathomechanisms of its formation, we divide effusions into two basic types. Transudate pleural effusions have a low protein content. They are usually caused by a systemic problem, for example, by the process of increased filtration either with increased intravascular hydrostatic pressure or with reduced oncotic pressure (in hypoproteinaemia). The pleura is not affected by the pathological process; it remains normal. Transudate pleural effusions are unilateral or bilateral. Systemic disorders associated with transudates are summarized in Table 3.2. Exudate pleural effusions have a high protein content. It usually occurs in diseases of the pleura and lungs, in which there is an increase in the permeability of the pleura, for example, in inflammation, or in an impairment of resorption (for example, by blocking lymphatic drainage). Exudate pleural effusions are usually unilateral. Possible causes of both types of pleural effusion are listed in Table 3.2.

Table 3.2. The main causes of transudate and exudate pleural effusions

Transudate	Exudate
Cardiac failure	Parapneumonic effusion
Constrictive pericarditis	Tuberculosis
Nephrotic syndrome	Connective tissue and autoimmune disorders
Acute glomerulonephritis	(rheumatoid arthritis, systemic lupus
Uraemia	erythematosus, vasculitis, sarcoidosis)
Liver cirrhosis with portal hypertension	Amyloidosis
Dressler syndrome, post-thoracotomy	Pancreatitis, subphrenic abscess
syndrome	Benign ovarian tumour (Meigs' syndrome)
Ovarian hyperstimulation syndrome	Malignant effusions (primary lung cancer
Hypothyroidism (also exudate)	and secondary malignities)
	Para-malignant effusions (associated with
	malignancy but without evidence of cancer
	cells in the effusion - for example, in the
	blockage of lymphatic vessels)
	Pulmonary embolus / lung infarction

Transudates are mostly bilateral (except for effusion in liver cirrhosis), while exudates are more often unilateral. Fluid in the pleural cavity (fluidothorax) can also be of a different nature than effusion (exudate or transudate); in the case of blood accumulation, we speak of **haemothorax**, lymph accumulation is called **chylothorax**. They most often occur when the continuity of a blood vessel (blood or lymphatic) is disrupted, for example, in an injury or for disease reasons (e.g., cancer).

CLINICAL FEATURES

The most common subjective symptom of the presence of pleural effusion is **dyspnoea,** caused by compression of the lungs on the affected side, depending on the extent of the effusion. **Pleural chest pain** associated with respiratory excursions and alleviated lying on the side of the sick side, as well as **unproductive cough** may be present. The latter two symptoms are related to irritation of the parietal pleura and tend to be more marked in inflammatory diseases

(pleuritis) and, conversely, less in non-inflammatory causes when the dyspnoea dominates. Extremely large pleural effusions are associated with mediastinal displacement in the contralateral direction and possible compression of large veins with a reduction in right ventricular filling and a consequent reduction in cardiac output with **hypotension and circulatory collapse**. Objective findings in a general physical examination may detect dyspnoea, tachypnoea, or cyanosis. On the chest, on the affected side, auscultation **breathing is weakened to inaudible**, **dull percussion** on the chest and weakened fremitus pectoralis. In the case of large effusions, the expansion of the intercostal spaces may be visible - *expansio hemithoracis*. In addition to the described manifestations within the pleural syndrome, there are also symptoms and objective findings depending on the present underlying disease, which is the cause of effusion (according to Table 3.2.).

DIAGNOSIS

The basic examination among imaging methods is a **chest X-ray** in posteroanterior and lateral projection. It detects the presence of fluid in the pleural cavity and is sensitive from 200-300 ml of fluid. Pleural effusion is displayed characteristically as a dense white shadow with a concave upper edge. Small effusion can cause only a blunting of a costophrenic angle, whereas very large effusion cause „whitening out“ of an entire hemithorax, with a shift of the mediastinum to the opposite side. A more sensitive examination for the detection of a smaller amount of fluid - already around 50 to 100 ml - is **ultrasonography**, which can also show possible fibrin septa, loculated effusions and pleural thickening. We also use it to navigate during pleural puncture. Sometimes in the setting of pleuritis, loculation of fluid may occur within the fissures or between the pleural layers (visceral and parietal). **Computed tomography** examination allows accurate localization of effusion (including complicated, loculated effusions), determine the nature of fluid content according to density (haemothorax, empyema) and is helpful in diagnosing lung and pleural diseases as causes of effusion (inflammatory infiltrates, tumours, systemic conjunctivitis and other).

Each pleural effusion should be verified by **diagnostic pleural puncture (thoracocentesis)**. This is the key investigation. After assessing its macroscopic appearance (serous, purulent, sanguinolent, milky appearance in chylothorax), the obtained punctate is examined biochemically, cytologically and through microbial cultivation.

Basic **biochemical tests** will allow the exudate to be distinguished from the transudate. The determination of the concentration of total proteins and albumin, the activity of lactate

dehydrogenase in the effusion, as well as the ratio to the serum values of these parameters, is used for this, according to the so-called Light's criteria, summarized in Table 3.3.

Table 3.3. Light's criteria for distinguishing exudate and transudate

	Exudate	**Transudate**
Total protein	> 30 g/l pleural fluid/serum ratio > 0,5	≤ 30 g/l pleural fluid/serum ratio ≤ 0,5
Lactate dehydrogenase (LDH)	pleural fluid/serum ratio > 0,6	pleural fluid/serum ratio ≤ 0,6
pleural fluid LDH	> 2/3 of the upper reference limit in serum	< 2/3 of the upper reference limit in serum

A **gradient of serum and puncture albumin** can also be used. In the exudate, a pleural-serum albumin gradient is < 12 g/L. Other investigated biochemical parameters in the pleural punctate are glucose concentration (decreases in bacterial infections), the concentration of triacylglycerols or cholesterol (high in chylothorax), and amylase activity (increased in the punctate in pleuritis induced by pancreatitis). Increased **adenosine deaminase** (ADA) activity is found in tuberculosis effusions. In addition, we send a sample of puncture in a sterile tube for **culture examination** for non-specific flora and another sample for culturing *mycobacterium tuberculosis*. **The cytological examination** aims to prove the presence and type of tumour cells in the punctate; it can also detect mesothelium, erythrocytes, or inflammatory elements – polymorphonuclear cells and lymphocytes.

Pleural biopsy is required for definitive morphological evidence of structural pleural disease (secondary and primary malignancies, amyloidosis, sarcoidosis). We perform this optimally in a targeted manner, most often as part of a **video-assisted thoracoscopic surgery**.

TREATMENT

Treatment of pleural effusions focuses on alleviating symptoms, treating the underlying disease, and preventing the recurrence of effusions. In the case of large effusions, the relief of

symptoms is achieved by **pleural aspiration**, at the beginning of which it is also possible to obtain samples for diagnostic examinations of the punctate. Alternatively, it is possible to introduce **chest drainage** in some workplaces. The therapeutic effect of the underlying disease is crucial for the overall causes of transudates (diuretic administration, protein supplementation, albumin administration, and other treatments according to the type of underlying disease). **Parapneumonic effusions** are common causes of exudates. Uncomplicated parapneumonic effusions usually respond to anti-infective treatment of pneumonia. If a parapneumonic effusion is complicated by the development of **thoracic empyema** (when pH of the punctate is < 7.2), the conservative procedure is unsuccessful and surgical intervention – thoracic drainage or removal of the empyema sheath – decortication is necessary, together with the administration of broad-spectrum antibiotic treatment. In malignant pleural effusions, causal treatment is systemic antitumor therapy (chemotherapy or hormonal or biological therapy). However, due to the frequent recurrences and rapid progression of malignant effusions, procedures to prevent the recurrence of exudates play an important role. Palliative surgery, in which the formation of adhesions over the entire area of the parietal and visceral pleura and the obliteration (extinction) of the pleural cavity is achieved, is called **pleurodesis**. It can be performed by introduction of an irritant (e.g., talc) into the pleural space following video-assisted thoracoscopy or drainage (**talcage**). Surgical pleurodesis is achieved by abrading the pleura or by removing it (**pleurectomy**).

4 LUNG CANCER

Lung cancer

- Is the **most common malignancy of the lungs**. It is a malignancy arising from epithelial cells and neuroendocrine cells of the bronchial tree and alveoli. The risk factors are **tobacco smoking** and **exposure to asbestos, radon gas** and other chemical carcinogens, as well as a genetic predisposition

- Diagnosis is based on medical history, clinical examination, **imaging** (X-ray, computed tomography), **bronchoscopy examination** and acquisition of material for **histological** or **cytological examination**

- Before deciding on the possibility of **surgical treatment,** it is necessary to know the **histological type** of the tumour, the clinical stage (**staging**) and to assess the risk of surgery for the patient also lung function testing, arterial blood gases and consideration of associated diseases

- Based on the histological type, staging and patient's performance status, modalities of **oncological treatment** are indicated - **radiotherapy**, systemic **chemotherapy,** and **biologically targeted treatment**, with the intention of curative or palliative treatment.

- **Palliative treatment of cancer complications** focuses on the treatment of **superior vena cava syndrome by anti-oedema treatment**; in the case of **malignant pleural effusion, pleurodesis** is indicated, and in the case of **tumorous obstruction of the large airways**, **recanalization** can be achieved by electrocautery, laser or stenting

DEFINITION AND CLASSIFICATION

Lung cancer (primary lung cancer, bronchogenic carcinoma) is a disease in which uncontrolled growth of malignantly transformed bronchial epithelial cells in the lung occurs. It is usually a heterogeneous bronchial and lung parenchyma tumour containing malignant cells with different degrees of differentiation or different histological types.

Although the pathology of lung cancer is complex, for clinical purposes, the disorder is classified into two groups – **small-cell lung carcinoma** (SCLC) (20% of cases) and **non-small-cell lung carcinoma** (NSCLC (80% of cases). The WHO classifies lung carcinomas into multiple groups, and all histological types except for small-cell are subject to NSCLC (Table

4.1.). Of these, adenocarcinoma (40%), and squamous cell carcinoma (25-30%), followed by large cell carcinoma (3-9%), are the largest. When the tumour contains SCLC cells of another histological type, it is referred to as a combined cancer. Small cell carcinoma, together with pulmonary carcinoid (the second most common primary lung tumour, originating from neuroendocrine cells of the bronchial mucosa) due to different immunohistochemical properties, forms a subset of epithelial tumours of neuroendocrine origin.

Table 4.1. Basic histological types of lung cancer

Histological type
Squamous-cell carcinoma
Adenocarcinoma
Large-cell carcinoma
Small-cell lung carcinoma
Sarcomatoid carcinoma
Salivary gland-like carcinoma

EPIDEMIOLOGY

Lung cancer is a global problem, and while it was a rare disease at the beginning of the 20th century, it became a **„top killer“** at the end of it. Currently, it accounts for 13% of all new cancers and is responsible for 1.3 million cancer deaths worldwide. It is a lethal disease, with only 25% of patients surviving one year and only 7% surviving five years from diagnosis. 9 of 10 lung cancer cases are caused by cigarette smoking. The incidence of the disease is highest in „western” countries (Europe, North America); however, also in lower-income countries, there is a gradual increase in incidence due to the growing smoking epidemic.

Lung cancer is the **most common cause of cancer deaths in men in the Slovak Republic** (almost 25%) and second in women (nearly 10%). The disease is diagnosed over a wide age range of 35-85 years, with most cases occurring between the 55s and 80s. Incidence in men is relatively stable (around 50 cases per 100,000 inhabitants) with a slight tendency to decline. Although the incidence is lower in women than in men, it has been increasing in the

long term (12 per 100 thousand inhabitants) and with it also mortality. The increasing prevalence of smoking in women during the 20th century and the impact of involuntary, passive smoking are one of the most important factors for this increase. The high mortality rate of the disease is also because, despite the introduction of new diagnostic methods, most cases (approximately two-thirds) are detected only in advanced stages where treatment options are limited.

AETIOLOGY

Several **endogenous and exogenous factors** contribute to the disease. Among the **endogenous causes** contributing to the individual susceptibility of the individual, we may mention the increased activity of cytochrome P450, which increases the production of carcinogens from cigarette smoke. An important antioxidant enzyme is glutathione-S-transferase, whose reduced activity is associated with slowed detoxification of aromatic hydrocarbons. Also described are gene mutations and chromosome aberrations associated with an increased incidence of lung cancer, for example, deletion of 3p21, as well as mutations of the tumour suppressor gene p53 and others. Regarding genetic factors, a **family history** of lung cancer can play a role in the increased risk of disease. There is also an increased incidence of lung cancer in patients with diffuse lung fibrosis (e.g., idiopathic pulmonary fibrosis), and so-called **scar carcinomas** can occur in areas of fibrosis also resulting from previous tuberculosis.

Tobacco smoking (mostly cigarette smoking) is the leading cause of lung cancer. Up to 90% of cases of the disease are caused by this factor, and about 10-20% of all smokers become ill. In Slovakia, according to statistics, about 1.6 million people smoke, but in the age group of young people between the ages of 15-29 years, up to 52% of the population. Of the total number of smokers, approximately 20-30% are women. By comparison, in the United States and in the UK, only about 20% of the adult population smoke. The risk threshold is considered to be 150-200 thousand cigarettes for life, which corresponds to 20 pack-years, but the individual susceptibility varies. The term pack-year is explained in detail in Chapter 2 (COPD). A 'heavy smoker' is defined as a person with an exposure of 20 or more pack-years, who has smoked 20 cigarettes a day for at least 20 years, or 40 cigarettes a day for 10 years. A heavy smoker has about a 10-15% chance of developing lung cancer and is 20 times more likely to develop the disease than non-smokers. The duration of exposure is a more significant risk

factor than the number of cigarettes alone; if the daily number of cigarettes is doubled, the risk will double, but if the number of years of smoking doubles, the risk will be 5-6 times higher. **Passive smoking**, also referred to as involuntary, also demonstrably increases the risk of disease, but unlike active smokers, it cannot be quantified. There are more than 60 **carcinogens** responsible for cancer in tobacco smoke. Most important are polycyclic aromatic hydrocarbons, aromatic nitro compounds, tobacco-specific nitrosamines, aldehydes, carbon monoxide, benzene, toluene, phenols, and metals such as chromium, nickel, cadmium, and many other pollutants are also used.

An important proven risk factor for the disease is **radon.** Radon (^{222}Rn) is an inert gas produced as a decomposition product of uranium and radium, its half-life is 3.8 days, and its further decay generates radioactive elements that ionize genetic material by emitting ionizing alpha radiation and lead to mutations. Most often, it penetrates the living space from unsuitable building materials and from the geological subsoil. In the United States, radon gas exposure is the second leading cause of lung cancer. The basic protection is the ventilation of living areas and thorough insulation of the foundations of buildings.

Asbestos exposure is most often associated with the risk of asbestosis or malignant mesothelioma but is also a risk factor for lung cancer. Tobacco smoking and concomitant exposure to asbestos have a proven synergistic effect on the disease. **Air pollution** is also an important factor, as evidenced by an increase in lung cancer incidence in urbanized and industrialized agglomerations with significant air pollution, and imperfect biomass combustion is also a major cause. Carcinogenic loads in the work and environment are not negligible. Besides ionizing radiation (including its medical use), a wide range of substances such as inorganic compounds arsenic, nickel, cadmium, chromium, dimethyl ether, and polyvinyl chloride are used.

Furthermore, a lack of dietary fruit and vegetables can contribute to disease development.

DIAGNOSIS

Clinical features

The clinical picture of the disease is diverse, and we can classify the symptomatology of the disease into general symptoms of malignant disease, then chest symptoms, which can be divided into "early" symptoms of local lung involvement and "late" symptoms of a locally advanced tumour, symptoms related to metastatic affection of distant organs and paraneoplastic syndromes. It is not possible to rely on symptomatology for early diagnosis of lung cancer, the disease may not manifest for a long time, and even minimal symptoms may indicate advanced disease.

General symptoms of malignant disease

General symptoms or non-specific systemic manifestations of malignancy are referred to as general paraneoplastic symptoms since they are not caused by the spread of the primary tumour or its metastases. Their causes are multifactorial, most often caused by the production of biologically active substances by malignant cells (cytokines, growth factors, interleukins). The most common manifestations include anorexia, nausea, weight loss in tumour cachexia, weakness, orthostatic hypotension, and low-grade to high-grade fever.

Initial symptoms of local lung involvement

Cough is the most common symptom but may be absent in more than 20% of cases. A newly occurring cough in persons who do not have chronic bronchitis or other previous respiratory problems is considered to be subacute for a duration of more than 3-4 weeks and is indicative of a diagnostic assessment of its cause, at least with a chest X-ray. On the other hand, many smokers have chronic bronchitis, which is manifested by cough, and in most cases, does not indicate the presence of cancer. However, a warning signal is a change in the character of a cough (change in frequency, intensity, irritability, occurrence during the day, expectoration).

A less common symptom that forces the patient to see a doctor is **haemoptysis**. It occurs mostly in endobronchial space, growing or spreading tumours and is caused by erosion of the bronchial vessel. At the time of diagnosis, it is present in about 20% of patients and may have the character of lesser amounts of fresh or clotted blood or sputum blood strips. At other times, sputum may only have a pinkish appearance.

Lung cancer is very commonly found in patients treated for **recurrent pneumonia** at the same site. Pneumonia with slow or incomplete regression of the infiltrate on the chest X-ray may be suspected of malignancy. This secondary so-called post-obstructive pneumonia is caused by the external pressure of the tumour on the bronchial lumen or by its partial obstruction of the intraluminal growing tumour.

Symptoms of locally advanced lung cancer

Chest pain, due to the lack of nociceptive receptors in the lungs and visceral pleura, only occurs when the tumour grows into the parietal pleura, thoracic wall, intercostal nerves, and mediastinum. It can also be caused by osteolysis of ribs or sternum by tumour or its metastases. Pleural pain is relatively well localized, and the affected person attains relief in a lying position on the diseased side. When a pleural effusion is formed, the pain is more of a pressure character and is accompanied by shortness of breath. **Pancoast´s tumour** is a type of cancer that is localised in the superior sulcus of the lung and invades through the chest wall, proximal ribs, muscles, and brachial plexus. It occurs in about 5% of cases of lung cancer, and the symptomatology of brachial plexus C8 and Th1 nerve root infiltration includes weakness and atrophy of small hand muscles, pain and paraesthesia of the forearm and severe shoulder pain. Patients are often mistakenly initially examined and treated by an orthopedist or neurologist before lung cancer is diagnosed. This type of tumour also often infiltrates the sympathetic paravertebral chain, which leads to the development of **Horner's triad of eye symptoms** – ptosis, miosis, and enophthalmos. This **Horner's syndrome** is complemented by ipsilateral hemifacial anhidrosis (due to stellate ganglion involvement).

Dyspnoea is another symptom that indicates advanced disease but is not specific to lung cancer. It may be caused by obstruction of the main bronchus or by the external pressure of the tumour on the bronchus, resulting in atelectasis of part of the lung parenchyma. Other causes of dyspnoea include the involvement of lymphatic vessels in the lung interstitium – carcinomatous lymphangiopathy, the accumulation of malignant effusion in the pleural cavity and/or in the pericardium, concomitant COPD, diaphragm paresis (when infiltrating the **phrenic nerve**) or embolism in the pulmonary artery (haematological complication in lung cancer). In the case of cancer infiltration or pressure on the **recurrent laryngeal nerve** (due to its anatomical course more often to the left), the patient develops unilateral vocal cord palsy and **hoarseness of the voice (dysphonia)**, which may be mistaken for laryngitis, but there are no signs of upper respiratory infection and sore throat. It is called a red flag symptom with the

need for urgent diagnosis. Another nerve that can be affected is the **phrenic nerve** resulting in paresis (and elevation) of the diaphragm on the affected side. This may be asymptomatic; at other times, the patient may experience a feeling of shortness of breath and, rarely, **singultus** may occur when nerve irritation occurs. **Dysphagia** is a rare symptom and occurs when a tumour causes pressure on the oesophagus or its infiltration. A serious complication is a tracheoesophageal fistula, where the ingested food and fluids pass into the airways.

Obstruction of the superior vena cava (by cancer or by thrombosis) causes engorgement of the upper body with facial and neck oedema (Collar of Stokes), headache, dyspnoea, distended pulseless jugular veins and enlarged collateral veins over the chest and arms. This is called **superior vena cava syndrome.** The patient also has blurred vision, and conjunctival chemosis is present.

Symptoms of extra thoracic metastases

Lung cancer can spread metastases to various organs, most commonly involving the mediastinal, supraclavicular, and other lymph nodes, liver, bone, brain, skin, and adrenal, but often haematogenic lung metastases. The size of the primary tumour may not correlate with the extent of metastatic involvement. **Small cell carcinoma** tends to metastasize early in the clinical course, and symptoms of metastatic involvement are often the first manifestation of the disease. Approximately 25% of patients develop **bone metastases**. The spine, ribs, skull, pelvic and long bones of the limbs are most affected, and osteolytic lesions are typical. Their first manifestation is pain and pathological fracture**. Central nervous system metastases** are present in about 40% of cases and are the most common in SCLC and adenocarcinoma. Symptomatology is often a combination of focal symptoms and intracranial hypertension, with limb movement disorders in terms of hemiplegia, headache, nausea, blurred vision, psychological changes, and consciousness disorders. Cerebellar metastases may be manifested by ataxia. Weakness and paraesthesia of the lower limbs and possible bladder and intestinal dysfunction are suspected of spinal cord involvement. **Lymph node metastases** may be manifested by accidental swelling of the lymph node, most commonly in the cervical and axillary region. Relatively frequent but long asymptomatic is metastatic involvement of the liver and adrenal glands. The manifestations of liver metastases are present only after extensive disability and include weight loss, anorexia, epigastric pain, later ascites, and icterus.

Paraneoplastic syndromes

Paraneoplastic syndrome (PS) is a set of clinical and metabolic symptoms irregularly associated with a malignant tumour that are not caused by the direct spread of the primary tumour or its metastases. They are manifested at sites distant from the tumour and its metastases. In addition to the general symptoms, they include a variety of endocrinopathies, haematological, neurological, ocular, skin, joint and renal symptoms. At the time of diagnosis, some of them are present in 15-20% of patients and are most often associated with small cell carcinoma. It is important to distinguish them because, in many cases, these PS precede clinical manifestation of the tumour and are the first sign of the disease.

Of **haematological PS**, **anaemia of chronic disease** is common, occurring in about 20% of cases. On the contrary, **polyglobulia** is due to an increase in erythropoiesis in ectopic erythropoietin-producing tumours. **Thrombocytosis** is quite common in all types of lung cancer in malignant diseases, but autoimmune thrombocytopenia may also occur. **Reactive leucocytosis** can reach high levels, referred to as the so-called leukemoid reaction. Malignant diseases are often accompanied by **hypercoagulation** conditions, and up to one-fifth of patients may develop disseminated intravascular coagulation (DIC). An important symptom is also thrombophlebitis migrans (Trousseau's sign).

Paraneoplastic endocrinopathies are common PS. They are caused by ectopic production of hormones in tumour or metastasis. **Hypercorticism** (Cushing's syndrome) occurs in the ectopic production of adrenocorticotropic hormone (ACTH) and is most often manifested by hypertension, muscle weakness, and hypokalaemia. **Hypercalcaemia** often occurs in non-small cell tumours, and in cases where osteolytic metastases are absent, it is considered PS and is most often caused by the production of the parathyroid hormone-related peptide. The **syndrome of inappropriate antidiuretic hormone secretion** (SIADH) leads to serum hypoosmolality (below 280 mosmol/L) and urine hyperosmolarity (greater than 500 mosmol/L) and is manifested by headache, weakness, nausea, vomiting, dizziness, consciousness disorders, convulsions, and coma. It is mostly associated with small-cell lung cancer.

Neurological PS can include various peripheral neuropathies, then neuromuscular PS such as Lambert-Eaton myasthenic syndrome, dermatomyositis and polymyositis, spinal cord PS (necrotizing myelopathy and amyotrophic lateral sclerosis), as well as central PS (subacute cerebellar degeneration, limbic encephalitis, dementia).

Dermatologic PS include acanthosis nigricans, eruptive seborrheic keratosis, ichthyosis acquisita, erythroderma, pemphigus vulgaris, but also pruritus. Among the **ophthalmologic PS**, mention may be made of retrobulbar neuritis and paraneoplastic retinopathy, leading to a

gradual loss of vision. Hypertrophic pulmonary osteoarthropathy, characterized by a triad of symptoms – mallet fingers, periostosis, and arthritis, as well as Jaccoud's arthropathy with ulnar deviation of the fingers and subluxations in metacarpophalangeal joints can be included in the **joint PS**.

Investigations

The diagnosis of the disease is complex and consists of medical history, clinical examination, and subsequent imaging methods (especially chest X-ray and computed tomography), which most often lead to a working diagnosis of lung tumour, but definitive confirmation of the diagnosis requires morphological examination (histological or cytological). The final diagnosis must include the **histological type of tumour**, extent of involvement – **clinical stage** and patient's **performance status**.

When taking a **medical history,** in addition to looking for the above symptoms, we focus on exposure to risk factors – smoking, occupational exposure to chemicals, and ionizing radiation. In the **family history,** we look for the occurrence of this disease in the family (blood relatives).

The physical examination can often reveal a normal chest finding, but there may be weakened or disappeared breathing on the affected side and dull percussion for extensive pleural effusion or atelectasis, tracheal (bronchial) breathing, or accentuated crackles in post obstructive pneumonia. If lung cancer develops in a patient with a known diagnosis of COPD (smoking as a common risk factor), emphysema or bronchitis may be present. It is also necessary to examine the lymph nodes in the neck, supraclavicular area and the axils. Examination of the liver with a finding of hepatomegaly with an uneven edge may indicate metastatic involvement.

Chest X-ray is a basic imaging examination and should be performed in posterior (PA) and lateral projections. Radiological findings in lung cancer are very diverse and include both direct and indirect signs of tumour. Lung tumours may have the character of a peripheral lesion in the pulmonary parenchyma, which may be focal and vary in size from the coin diameter node, the so-called "coin lesion", up to large tumours. These may be bounded or with uneven edges. Centrally located tumours are imaged as hilar infiltrates. Tumours may also be accompanied by atelectasis of the anatomically delimited part of the parenchyma (lung lobe and whole lung wing), sometimes by so-called post-obstructive pneumonia, pleural effusion, unilaterally elevated diaphragm, and mediastinal masses. If the tumour breaks down and a

cavity is formed in its centre, a cavitated lesion (sometimes called the Jores cavern) is displayed on the X-ray. It is characteristic of a squamous-cell carcinoma.

Computed tomography (CT) imaging – is an examination with a higher sensitivity than a chest X-ray (detection of lesions from 0.5 cm in size compared to lesions > 1 cm on X-ray). The examination is performed using a contrast material which enhances the contrast of inflammatory and tumour lesions. The scan defines the position and size of the primary lesion, determines the stage of the disease (staging), and, together with other examinations, helps to assess resectability and surgical treatment options. The stage is evaluated according to the extent of involvement, the presence of suspected pathologically enlarged lymph nodes (> 1 cm) and distant metastases in the chest area. CT of the chest usually also captures part of the upper abdominal cavity, where distant metastases in the liver and adrenal glands are eventually detected.

Magnetic resonance imaging (MRI) – is less used but is useful when contrast agents cannot be administered in CT and better distinguishes tumour growth into the mediastinal organs, thoracic wall, and infiltration of nerve structures (such as Pancoast tumour).

Positron emission tomography (PET-CT) – is an increasingly available method of imaging not only tumour but also tumour-affected lymph nodes and distant metastases but is not suitable for detecting brain metastases.

Other examinations include the **abdominal ultrasound** examination for the detection of metastasis in the liver and retroperitoneum organs and **scintigraphy** (radioisotope bone scans) of the skeleton for the diagnosis of bone metastases. If neurological symptoms are present, **CT and/or MRI of the brain** are necessary to detect cerebral metastases.

Bronchoscopy (fibro-bronchoscopy) – represents the basic examination method in the lung cancer diagnostic algorithm. It allows not only visualization of endobronchial spreading tumour (the extent of spread must be evaluated for staging) but also a collection for cytological or histological examination of the tissue. Depending on the local condition (tumour growth and risk of bleeding), there is a possibility to obtain a sample by biopsy forceps for histological examination or for cytological evaluation by brushing or bronchial lavage. In the endoscopic image, we can see direct changes (endobronchial tumour growth in the form of exophyte or areal infiltration of the mucosa and bronchial wall) or indirect, caused by the pressure of tumour mass or enlarged lymph nodes on the bronchus externally (bronchial deformation and narrowing). **Endobronchial ultrasound** (EBUS) is a special method which enables the visualisation of mediastinal lymph nodes and peribronchial lesions and obtaining a sample by a biopsy needle.

If fibrobronchoscopic examination has not been able to obtain representative material for determining the histological type of tumour (for example, because of its peripheral location), consideration should be given to using other tissue collection methods. Peripheral tumours seen on chest X-ray may be accessible by **percutaneous needle biopsy** under radiological guidance (ultrasound or CT). **Video-assisted thoracoscopy** (VATS) allows targeted biopsy not only of the lesion in the lung parenchyma but also on the pleura and, to a limited extent, of the mediastinal structures). **Mediastinoscopy** is especially suitable for the collection of enlarged mediastinal lymph nodes. Last but not least, **sputum cytology** can be useful. It can be performed repeatedly (with positivity in about 40% of cases), and it is particularly useful in patients unfit for invasive tests. If the available methods have not been able to determine the type of tumour, the **surgical procedure – thoracotomy** and lung resection or biopsy is indicated after evaluation of the patient's operability (listed in the Treatment section).

Blood tests allow the determination of concentrations of several types of **oncomarkers (tumour markers)**. In small cell carcinoma, the oncomarker is NSE (neuron-specific enolase) or pro-GRP (pro-gastrin-releasing peptide), in the case of NSCLC, it is CEA (carcinoembryonic antigen), CYFRA 21-1, or SCCA (squamous cell carcinoma antigen). Examination of tumour markers is not a substitute for histological verification of the tumour, but it is important in monitoring the activity (repeated collection of an increased marker over time) of a known and properly diagnosed disease.

TREATMENT

In the treatment of lung cancer, the following options are considered:

- **surgical treatment**
- **radiotherapy** (treatment with ionizing radiation) – represents regional treatment; it can be applied externally or less often in the form of brachyradiotherapy by introducing a radiation source into the bronchi
- **chemotherapy** applied systemically
- systemically applied **biological targeted therapy**

The above-mentioned treatment options may be applied to achieve one of the objectives:

- **curative** – the point is to achieve disease remission – a condition without a detectable tumour in the body

- **palliative** (the purpose is favourably influencing the manifestations of the disease, improving the quality of life, prolonging survival) if it is not possible to achieve removal of the tumour from the body – advanced stage of the primary tumour, the presence of distant metastases.

Treatment depends on the histological **cell type**, the clinical stage (**staging**) of the disease and the fitn**ess** of the patient (**performance status – see Table 4.2.**).

Table 4.2. Performance status (WHO performance scale)

Grade	Criterion
0	Fully active and able to carry out all normal activities
1	Ambulatory and able to carry out non-strenuous activities
2	< 50% in bed during waking hours and capable of self-care
3	> 50% in bed during waking hours and capable of only limited self-care
4	Bed bound and completely dependent

The classification of clinical stages - staging - varies between SCLC and NSCLC.

Small cell lung cancer – SCLC – uses a simplified classification for two clinical stages:

1**. Limited disease (LD)** – the extent of the tumour is limited to one lung side (mediastinal lymph nodes and pleura may or may not be affected, e.g., by pleural effusion), which may be entrapped in a single radiation field during external radiotherapy

2. **Extensive disease (ED)** – all other forms of the disease

Systemic chemotherapy (platinum derivatives – cisplatin, carboplatin, combined with other cytostatic, e.g., etoposide) is the basic treatment for SCLC in both stages of the disease. External **radiotherapy** in combination with chemotherapy is the standard procedure for limited disease. It can be given concomitantly with chemotherapy (**concomitant chemoradiotherapy**), which has better treatment results but with a higher incidence of side effects or is given after the end of chemotherapy. **Cranial radiotherapy** is given to patients (also with limited disease) for the prevention of cerebral metastases. Radiotherapy of bone metastases is of palliative importance in extensive disease in a patient with good performance status. As the SCLC is a highly malignant cancer that has usually disseminated widely by the time of diagnosis, surgery is not a treatment of choice.

For non-small cell lung cancer – NSCLC – the clinical stage of the disease is evaluated at the time of diagnosis according to the internationally valid **TNM** (tumour - nodus lymphaticus - metastasis) classification system. **T-staging** (T1-4) assesses tumour size in cm, distance from tracheal carina, invasion of structures such as pleura, thoracic wall, diaphragm, phrenic nerve, pericardium, spread to the mediastinum, large vessels, heart, trachea, oesophagus, vertebral bodies or establishing satellite nodes in the lungs. **N-staging** distinguishes whether only the ipsilateral intra-pulmonary and helical nodes, even the ipsilateral mediastinal, or even the contralateral hilar and mediastinal nodes or any neck nodes (scaleni, supraclavicular) are affected. **M-staging** assesses the presence of distant metastases, including the presence of malignant pleural effusion. Considering all staging items, the clinical stage, designated from I to IV, is subdivided into stages A and B at each stage. The presence of distant metastases – M1 means clinical stage IV, patients in stages I to III do not have distant metastases (M0).

The decisive issue in the therapeutic consideration of NSCLC is the possibility of **curative surgical treatment**. The possibility of **resectability** – the anatomical extent of the procedure with respect to the size and extent of tumour spread is considered. The gentlest option is lobectomy – removal of one lobe of the lung, pneumonectomy is also possible – removal of the whole lung on the affected side, and in the case of right lungs, bi-lobectomy is also possible. Clinical stages I to IIIA are resectable. In addition, the question of **operability** is important – whether the extent of the resection procedure is acceptable to the patient. The **operability** is determined by the results of the **lung function testing, arterial blood gases**, in case of borderline situations also the stress examination (for example by the 6-minute walk test) or the scintigraphy examination of the lung (ventilation-perfusion scan) and severity of comorbid disorders (heart failure, COPD etc.).

Systemic chemotherapy is applied with the objective curative following successful surgical resection as so-called **adjuvant** chemotherapy. In stage IIIA, the application of **neoadjuvant** chemotherapy is contemplated - to reduce tumour size prior to surgery. **Palliative chemotherapy** is applied in nonresectable stages IIIB and IV and inoperable patients in the lower clinical stages. When the patient's performance status permits, two cytostatic agents are administered at the same time – **combined chemotherapy** (a platinum derivative with another cytostatic). Commonly used drugs include ***gemcitabine, docetaxel, paclitaxel*** and ***vinorelbine***.

Radiotherapy applies as a potential curative or palliative modality at all stages of NSCLC. It is used mostly to control the following symptoms – pain associated with tumour

invasion, haemoptysis, bronchial obstruction by tumour and symptoms from extra-pulmonary metastases (e.g., cerebral, spinal). It can be administered alone or together with chemotherapy, either concomitantly – **concomitant chemoradiotherapy**, or **sequentially** – alternately.

Biologically targeted treatment of NSCLC acts on tumour cells by a mechanism other than standard chemotherapy – selectively at the molecular level interferes with various intracellular mechanisms. These precisely affect cell characteristics that are associated with the malignant nature of tumour growth, such as:
- inhibition of apoptosis (suppression of controlled cell death in tumour cell)
- the ability to rebuild vessels to provide nutrients to the tumour
- the uncontrolled proliferation of tumour cells
- ability to metastasize

There are several biologically targeted treatments for NSCLC. Overexpression of the **epidermal growth factor receptor** (**EGFR**) is a feature of some NSCLC. EGFR is a transmembrane protein with cytoplasmic kinase activity that transduces growth factor signalling to the cell. Examples of molecularly targeted treatments are tyrosine kinase inhibitors (e.g., ***erlotinib, gefitinib***), which are efficient in tumours with specific EGFR mutations. Another type of drug is ***bevacizumab***, the blocker of the **vascular endothelial growth factor (VEGF) receptor**, whose stimulation is responsible for the ability of neoangiogenesis to rebuild blood vessels. Biologically targeted treatment is currently a trend of major importance in cancer treatment, and there are several other promising drugs under development.

Palliative care aims to influence symptoms and improve the quality of life of lung cancer patients but does not affect tumour growth or survival. **Superior vena cava syndrome** is treated by palliative systemic chemotherapy in SCLC and palliative radiotherapy in NSCLC. Prior to its initiation, it is possible to alleviate the patient's symptoms by administering high-dose ***dexamethasone*** and administering diuretics. Palliative treatment of **malignant pleural effusion** consists in achieving obliteration of the pleural cavity after chemical inflammation induced by intrapleural administration of certain substances, such as sterile talcum (**chemical pleurodesis)**. The application of talc is performed after drainage of the pleural cavity, and it is necessary to achieve a good distribution of talk powder over the entire surface of the pleura. In the case of **obstruction of the large airways** (trachea, main bronchi) by an endobronchial growing tumour, the quality of life can be improved by **recanalization** of the affected section

(by laser, electrocautery, cryotherapy), possibly with subsequent **stent** insertion. In the case of persistent pain (despite radiotherapy), analgesic treatment is needed, starting with non-opioid analgesics, continuing with mild opiates, and ending with strong opiates (***morphine***).

5 INTERSTITIAL LUNG DISEASE

Interstitial lung disease

- **Interstitial lung diseases (ILDs)** are a heterogeneous group of over 200 diseases characterized by a degree of **alveolitis** and **fibrosis** of the interstitium; they share similar clinical, radiological, and functional characteristics
- The various classifications regard aetiologic, clinical and histopathological differences
- The treatment and prognosis differ according to the degree of the **reversible process, i.e., inflammation and irreversible process, i.e., fibrosis**
- The processes characterized by higher cellularization generally have a better prognosis and response to the treatment
- Clinical characteristics of ILDs include **progressive dyspnoea, dry cough, bilateral basal crepitations to rales, and central cyanosis** if chronic respiratory insufficiency is present
- Careful consideration of potential systemic diseases and exposition to a wide range of potential provoking factors must be undertaken in the diagnostic process
- The diagnosis requires performing **high-resolution computed tomography** (HRCT), **bronchoscopy** with bronchoalveolar lavage, and often **biopsy of pulmonary parenchyma**
- The treatment frequently includes **corticosteroids** or **immunosuppressants**, in the case of idiopathic pulmonary fibrosis, novel antifibrotic substances. The terminal stages of ILDs usually require **long-term oxygen therapy**. In some instances, **lung transplantation** might be the only curative option

DEFINITION AND CLASSIFICATION

Interstitial lung diseases (ILDs), also called diffuse diseases of the lung parenchyma or **diffuse parenchymal lung diseases** (DPLDs), are a heterogeneous group of over 200 diseases featuring non-infectious infiltration of interstitium and alveoli.

They are characterised by two processes: **alveolitis** (inflammation in alveoli) and **fibrosis of the interstitium**. The severity and prognostic of the ILD depend on the immunopathological process that determines the ratio between alveolitis and fibrosis. The outcome can lead either to reparation *ad integrum* (e.g., in sarcoidosis) or destruction of pulmonary architecture by a fibrosing process (e.g., in idiopathic pulmonary fibrosis).

Although ILDs share similar clinical and functional characteristics, they differ in aetiology, pathological and, to a certain degree, also in radiological patterns. Thus, the classification of ILDs is somewhat challenging; see Table 5.1.

Table 5.1. The classification of interstitial lung diseases.

Interstitial lung diseases (ILDs)

ILDs of known cause	**Idiopathic interstitial pneumonia (IIP)**	**Granulomatous ILDs**	**Other forms of ILDs**
Systemic (collagen / vascular disease)	**Major IIP:**	Sarcoidosis	Langerhans cell histiocytosis (Histiocytosis X)
Drugs	Idiopathic pulmonary fibrosis (IPF)	Hypersensitivity pneumonitis	Lymphangio-leiomyomatosis
Professional hazard	Idiopathic nonspecific interstitial pneumonia (NSIP)	Other	Other
Other	Respiratory bronchiolitis – interstitial lung disease (RB-ILD)		
	Desquamative interstitial pneumonia (DIP)		
	Cryptogenic organizing pneumonia (COP)		
	Acute interstitial pneumonia (AIP)		
	Rare IPP:		
	Idiopathic lymphoid interstitial pneumonia (LIP)		
	Idiopathic pleuropulmonary fibroelastosis (PPFE)		
	Unclassifiable IIP		

AETIOLOGY AND PATHOGENESIS

There are specific recognised causes of ILD. They include inhalation antigens, non-inhalation antigens, circulatory disorders, cancer, and infectious agents. Inhalation of noxious agents is often linked to professional exposition. Inorganic dust is a causal factor in silicosis, asbestosis or other pneumoconioses. Organic dust can lead to hypersensitivity pneumonitis, farmer's lungs, pigeon breeder's lungs and other specific diagnoses. A similar pattern can be observed in the inhalation of irritant gases like gases in chemical warfare or ozone. Non-inhalation agents include medication (e.g., antiarrhythmic drug amiodarone), illegal drugs (heroin, cocaine), poisons (e.g., herbicides), and treatment methods like radiation or oxygen therapy. Circulatory disorders like pulmonary congestion in chronic left heart failure or acute respiratory distress syndrome may likewise result in a fibrotic transformation of the tissue. Interstitium can also be affected in neoplasia, e.g., lymphangitis carcinomatosa, bronchioloalveolar carcinoma, infiltration in leukaemia or lymphoma. Also, infectious agents can be responsible for the fibrotic reconstruction of tissue.

However, in many cases, the origin of DPLD cannot be determined. DPLD can be part of systemic diseases that manifest in multiple organs: sarcoidosis, connective tissue disorders (e.g., rheumatoid arthritis, lupus erythematosus, systemic sclerosis), vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis) or hereditary conditions (e.g., tuberous sclerosis, neurofibromatosis).

Solitary pulmonary affection of unknown origin is typical for idiopathic interstitial pneumonia (IIP) and some rare disorders like lymphangioleiomyomatosis, alveolar proteinosis or pulmonary histiocytosis X.

The **main characteristic of ILD is the remodelling of the distant airspaces leading to impaired gas exchange**. This remodelling used to be attributed to persistent alveolar inflammation. Nevertheless, recently it is thought to be more a result of aberrant healing of tissue injured by some factor (e.g., infection, radiation, environmental exposure). The damage to the epithelium, endothelium, basal membrane, and interstitium provoke inflammation characterised by increased inflammatory cytokines. They influence the interplay between inflammatory and mesenchymal cells.

Dysregulation of inflammatory mediators, mostly in the sense of increased type I cytokines (IL-4, IL-5, Transforming growth factor beta (TGF-β) and a decrease of type II cytokines, e.g., interferon-γ (IFN-γ), promotes dysregulation of fibroblasts and excessive

production of collagen, vimentin, and actin deposition of extracellular matrix in the interstitium.

It is important to note that although inflammation is present in many types of ILDs, not all lung inflammation results in fibrotic remodelling and fibrosis can occur in the absence of inflammation.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical features

Patients with ILD typically suffer from progressive breathlessness and a dry cough. They are quickly tired. There are characteristic end-inspiratory rales (velcro type). In later stages, hypoxemia presents as central cyanosis, sometimes with finger clubbing. There can be haemodynamic consequences such as signs of pulmonary hypertension and right heart failure with peripheral to generalised oedemas, hepatomegaly, and positive hepatojugular reflux. Haemoptysis accompanied by haematuria is a common finding in Goodpasture syndrome. An affection of skin, joints and other organs can be present in connective tissue disorders and sarcoidosis. The course of the disease can be chronic and progressive but also rapid and fulminant. Sometimes there is acute onset or acute exacerbation of the disease.

Investigations

History:

A detailed history is necessary to confirm or exclude exposition to environmental factors. Even though some subtypes of ILDs have no definite cause, there are some recognised risk factors like smoking or gastroesophageal reflux. History of medication can reveal that a medicament taken years prior can cause current disease, same as radiotherapy on the chest.

Laboratory findings:

In most cases of ILD, laboratory findings do not help establish a diagnosis. The exception is ILD in vasculitis, where a presence of **antineutrophil cytoplasmic antibodies (ANCA)** can be expected. In sarcoidosis, we may examine the levels of ACE (angiotensin-converting enzyme) and the concentration of **calcium** in blood and urine. In cases of pulmonary haemorrhage, **anaemia** can be observed. **Eosinophilic pneumonia**, acute or chronic, goes with an increase in the eosinophil count and eosinophilic cation protein (ECP). Hypersensitive pneumonitis can present with an increased concentration of class G of **immunoglobulins**.

Examination of arterial blood gases usually displays **progressive hypoxaemia** worsening markedly after physical effort. Initially, due to hyperventilation, it is accompanied by slight hypocapnia. However, in the late stages of the disease, after the depletion of compensatory mechanisms, hypercapnia develops.

Pulmonary function tests:

Pulmonary function tests serve to establish the diagnosis and estimate its progression and treatment success.

ILDs are typical diseases with **restrictive ventilatory impairment**. The fibrotic lung tissue is denser, less elastic, less compliant, and constricts deep inspiration. Thus, the main finding is a **reduction in VC**. RV may be normal or decreased. FEV1 tends to be proportionally decreased; therefore, **FEV1/FVC ratio is normal**, even slightly increased. More work of breathing is required to overcome the low compliance of pulmonary tissue. When the tidal volume is normal or decreased, the patient breathes more rapidly to avoid exhausting the breathing muscles.

Thickening of the interstitial tissue partially blocks blood gases diffusion. We measure gas diffusion by measuring the **transfer factor for carbon monoxide (TLCO)**. It is also called total (diffusing) lung capacity for carbon monoxide. Carbon monoxide is used as a substitute for oxygen because of its stronger bond to haemoglobin. The concentration of haemoglobin should always be reported in this examination. Fibrotic changes in the alveolar-capillary membrane lead to a **decrease in TLCO**.

The combination of reduced gas diffusion, pulmonary compliance and post-exercise hypoxemia allows voicing suspicion of ILD before clinical or radiological changes are noted.

Radiological findings:

A simple **chest X-ray** may be helpful to set a suspicion for ILD. It can portray smaller lungs with **reticular or reticulonodular infiltrates**. Nevertheless, a golden standard of imagining for ILD is **high-resolution computed tomography (HRCT)**. The identification of basic HRCT patterns plays a critical role at the beginning of the diagnostic assessment. The pattern and the distribution of HRCT lung changes may sometimes suggest a specific diagnosis. The same disease can also present with a plethora of HRCT patterns, and the same pattern can be observed in multiple ILDs.

Some of the typical HRCT findings include:

- **Reticular pattern** – net-like patterns resulting from thickening of interlobular and intralobular septa, mostly seen at the periphery, the end-stage fibrotic lung has a coarse reticular pattern and is associated with honeycombing

- **Ground-glass patterns** – ground-glass opacities (GGO) appear as hazy areas of increased opacity of the lung, not covering underlying structures; they can result from a thickening of alveolar septa or alveolar filling with fluid

- **Consolidation patterns** – an area where the consolidated lung obscures vessels, airspaces are filled with fluid (e.g., oedema, blood, or pus)

- **Nodular pattern** – multiple airspaces or interstitial nodules, well or poorly defined, varying in size (up to 3 cm in diameter)

- **Cystic pattern** – a round parenchymal lucency with definable walls may result from abnormal dilation of bronchial structures (i.e., traction bronchiectasis), alveolar spaces or focal destruction of lung parenchyma

- **Honeycombing** – cystic airspaces with thick walls, areas of destroyed parenchyma where natural architecture was lost

Bronchoscopy and bronchoalveolar lavage:

In bronchoalveolar lavage (BAL), saline aliquots are instilled via a bronchoscope into the subsegmental bronchus and fluid is then aspirated for cell analysis. BAL cellular components reflect the potential inflammation process in alveoli and interstitium, mostly in terms of macrophages, neutrophils, eosinophils, and lymphocytes.

According to cells in BAL, there are four types of ILD processes:

- **ILD processes with neutrophilia**: e.g., in IPF, asbestosis, systemic collagen diseases

- **ILD processes with lymphocytosis** (more than 35% of lymphocytes): e.g., LIP, sarcoidosis, berylliosis, drug-induced ILDs

- **ILD processes with eosinophilia** (more than 4% of eosinophils): e.g., pulmonary eosinophilia

- **ILD processes with mixed cellularisation**

In some cases, BAL can lead to a definitive diagnosis, e.g., alveolar proteinosis or malignancy. BAL also has prognostic value. In the case of IPF or connective tissue disorders diseases, BAL with more neutrophils means a poorer prognosis than BAL richer in lymphocytes.

Pulmonary biopsy:

The histological analysis provides information about the aetiology, activity, and reversibility of the process. Usually, it is an indispensable part of the diagnosis of ILD. It can be omitted only in the case if other diagnostic procedures combined offer a certain or at least probable diagnosis or in the case of a patient's refusal. It should be performed at the early stages of the disease, as the risk of complications grows in time. Also, a late-stage disease with fully developed fibrosis hinders correct diagnosis. There are several methods to obtain a tissue sample. Small samples can be obtained by **transbronchial biopsy** of the lung parenchyma of the flexible bronchoscope. A distinct subtype of transbronchial biopsy called cryobiopsy, a relatively novel procedure, enables obtaining larger specimens by using a cryoprobe, rapidly freezing the surrounding tissue and then extracting it. Larger samples can be acquired by surgical biopsy under general anaesthesia, preferably by **VATS**. The histological finding is not enough to establish a definitive diagnosis because the same histological patterns can be shared by one of the IIP, by a disease with a known origin or by connective tissue disorder.

TREATMENT OF ILD

Proper treatment requires precise diagnosis. If aetiology is known, the treatment should be causal, ideally eliminating the provoking factor (inhalation agent, medication). If the aetiology of the disease is not known, **pharmacological treatment with anti-inflammatory or antifibrotic properties** is used. The most common type of medication is **systemic corticosteroids**. They have strong immunosuppressant effects and an unfortunate overabundance of side effects like osteoporosis, diabetes, arterial hypertension, gastric ulcers, and mental disorders. The effectivity of pharmacological treatment is checked in intervals usually 3 to 6 months long, where symptoms, laboratory findings, radiological findings (chest X-ray, HRCT) and lung functions (VC, TLCO) are evaluated. If systemic corticotherapy (mostly ***prednisone***) is insufficient, other immunosuppressants may be considered (e.g., ***azathioprine, cyclophosphamide***). In cases of the fulminant course of the disease, a pulse treatment of high-dose corticosteroids is applied (e.g., ***methylprednisolone*** up to 1 g i.v. per day). Some ILDs are highly sensitive to corticosteroids with immediate effect (e.g., NSIP). Corticosteroids should be avoided in case there is no current inflammation, mainly in IPF. There are newly registered medications with antifibrotic effects for this indication (pirfenidone, nintedanib).

The terrain of interstitial disease is of high risk for any infection. Thus, any overlying **infection should be treated** promptly and adequately. **Avoidance of smoking** is generally recommended, particularly in ILDs with recognised tobacco links (Langerhans cell histiocytosis, RB-ILD). **Respiratory physiotherapy** should be included in the treatment program.

With the disease progression and development of chronic respiratory insufficiency, **long-term oxygen therapy** (LTOT) might be necessary. Late-stage ILD usually has a bad prognosis, and the only treatment modality, which improves survival, is **lung transplantation**. Early listing to the waiting list is recommended due to the extreme legal complexity of the process. Many patients die while awaiting transplantation because of the low availability of organ donors. Post-operative mortality in transplanted patients is high; 2-year survival is 70%, and 5-year survival is 50%.

IDIOPATHIC INTERSTITIAL PNEUMONIA (IIP)

IIPs are a subgroup of ILD that affect exclusively pulmonary tissue and have no recognisable aetiology, although some risk factors or hereditary traits were observed. There are six major IIPs.

Idiopathic pulmonary fibrosis (IPF)

IPF is a progressive fibrosing interstitial pneumonia of unknown aetiology in adults limited to lungs and associated with the histopathological and radiological image of **usual interstitial pneumonia (UIP)**. It accounts for 20-50% of ILDs and represents the most frequent and severe of the IIPs. It is considered a rare disease, with 3-9 cases per 100 000 persons in Europe and North America but slowly increasing. However, the burden of the disease is high; in Europe, around 40 000 new cases are diagnosed a year.

Despite unknown aetiology, several **risk factors** have been identified. IPF tends to occur in older age; two-thirds of patients are over 60 years old. The disease is more common in men than in women. Cigarette smoking is the most strongly associated risk factor despite many IPF sufferers being non-smokers. Several chronic viral infections have been investigated in the aetiology of IPF (Epstein-Barr virus, adenovirus, herpes virus, hepatitis C). Alas, no definite conclusions have been drawn. Gastroesophageal reflux (GER) may play a role in the pathogenesis of the IPF as micro aspirations of the gastroesophageal content could constitute a factor damaging the alveolar epithelium.

Clinical features of IPF are progressive dyspnoea, dry cough, and clubbing fingers; the onset of the disease is usually stealthy. Inspiration crepitations can be heard over the bases of the lungs, later progressing to velcro rales over all the lungs, rapid shallow breathing. If pulmonary hypertension develops, signs of congestive right heart failure may be observed.

The natural course of the disease has a very poor prognosis of overall survival of 3-4 years. Different **phenotypes** of IPF can be identified, with different disease progression rates, including rapidly progressive, familial, combined emphysema and pulmonary fibrosis, pulmonary hypertension, and that presenting with autoimmune features. In 5-10% of patients with IPF experience acute worsening of the state triggered by secondary complications such as infection, microaspiration, heart failure, and pulmonary embolism. These acute changes may be fatal or can cause irreversible deterioration of the condition. Acute exacerbation of IPF is acute worsening of respiratory symptoms with histopathological and radiological correlate of diffuse alveolar damage (DAD) with or without consolidations, and sometimes the cause cannot be determined.

Pulmonary function tests display restrictive ventilatory impairment often preceded by decreased diffusion capacity. BAL is characterised by a majority of neutrophils. Chest X-ray shows reticulation mostly at the basis and periphery of the lungs. Still, sometimes an X-ray may seem entirely physiological, which does not exclude the possibility of IPF. The key imaging method is HRCT, which can sometimes be sufficient to state the diagnosis of IPF in an adequate clinical context. HRCT findings can be concluded as a definite UIP, probable UIP, uncertain UIP or an alternative diagnosis. Typical patterns for UIP are the basal and subpleural distribution of changes, honeycombing with or without traction bronchiectasis. There is only minimal evidence of inflammation as GGO.

Diagnosis of IPF can be established when other causes of ILD are excluded; there is a typical clinical context and definite or probable pattern of UIP on HRCT. Matching clinical context includes age over 60 years, the absence of significant environmental exposition to risk factors and the absence of systemic collagen disease. If the diagnosis is dubious, a pulmonary biopsy is recommended.

For the **treatment of IPF**, none of the medications used in the past (corticosteroids, azathioprine, N-acetyl cysteine) is recommended anymore. New medications have been introduced lately. **Pirfenidone** is an antifibrotic substance that inhibits TGF-β. TGF-β is involved in cell proliferation and differentiation and has a crucial role in fibrosis. Pirfenidone also inhibits the synthesis of TNF-α, which has an active role in inflammation. **Nintedanib** is a low molecular weight inhibitor of tyrosine kinase. It competitively inhibits receptors for

platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF). In this manner, nintedanib inhibits signal cascades involved in the proliferation, migration, and differentiation of fibroblasts/myofibroblasts, which are most typical in the pathogenesis of IPF. **Systemic corticosteroids** are used in acute exacerbation of IPF. Other therapeutic procedures include treatment of gastroesophageal reflux, respiratory physiotherapy and LTOT if required.

Acute interstitial pneumonia (AIP)

AIP is a rapidly progressing pulmonary disease of unknown aetiology with the fast development of respiratory failure. It was the first recognised IIP by Hamman and Rich in 1944, thus the synonym Hamman-Rich disease. A typical histopathological image is diffuse alveolar damage (DAD) with hyaline membranes, which is the same as in adult acute respiratory distress syndrome (ARDS). The same clinical findings are present in acute exacerbation of IPF. There are no known aetiology or risk factors. AIP course sometimes includes recent sickness like viral infection of the upper airways with fever, shivers, and pain. Shortly, usually up to three weeks, there is severe dyspnoea with rapid progression of restrictive ventilatory impairment and a decrease in gas diffusion measurements. The diagnosis is set on clinical presentation, HRCT pattern of fog-like opacities. In BAL, there are neutrophils and amorphic material from hyaline membranes.

The treatment includes high doses of corticosteroids; often, ventilatory support is necessary. The prognosis is poor; mortality reaches up to 50%, usually in 1-2 months from the onset of the disease. Survivors of the first attack of AIP have frequent relapses, and the disease progresses to generalised interstitial fibrosis.

Cryptogenic organising pneumonia (COP)

COP was first described in 1983, and later the same unit was described as bronchiolitis obliterans with organising pneumonia (BOOP). It is a clinical and pathological syndrome usually secondary to another disease or exposition to a pollutant. Histopathologically, alveoli and terminal bronchioles are obliterated by granulation tissue. OP can manifest after infectious pneumonia, as a graft-versus-host reaction after lung transplantation, after radiotherapy on the chest, malignancies, or autoimmune diseases. The patients complain of productive cough of transparent sputum, occasional low-grade or high-grade fever, and weight loss. Sometimes, they are in vain treated by multiple courses of antibiotics. Diagnosis is established when a typical clinical finding and HRCT are present. HRCT displays consolidations and GGO in

peribronchial and peripheral areas. In BAL, there is a dominance of CD8+ T-lymphocytes. COP responds well to the treatment by corticosteroids.

Respiratory bronchiolitis with interstitial lung disease (RB-ILD)

RB-ILD occurs almost exclusively in smokers. Histopathologically, there is bronchiolitis with an accumulation of macrophages containing brownish pigment in the proximity of airways, and with septal fibrosis, a biopsy is therefore very helpful. In treatment, smoking cessation is the first step; in case of persistent symptoms, corticosteroids may be considered. The prognosis is excellent.

Desquamative interstitial pneumonia (DIP)

DIP is present in all ages. It has a strong association with smoking, exposition to pollutants and other diseases (autoimmune diseases, leukaemia). Histopathologically, there is a massive proliferation of macrophages in alveoli that are also washed out in BAL. The treatment is the same as in RB-ILD, avoidance of cigarettes and corticosteroids, and the prognosis is also good.

Nonspecific interstitial pneumonia (NSIP)

NSIP is a diagnosis defined by histological exclusion of other types of ILD. It has three subtypes: cellular, fibrotic, and mixed. Focal findings identical to NSIP can be observed in other conditions, like UIP. Thus, NSIP was once considered an early stage of UIP. NSIP may be idiopathic or may occur as a manifestation of systemic connective tissue disease, hypersensitivity pneumonia, drug-induced lung disease, and chronic interstitial lung disease complicating DAD. It can occur in every age group, even children. The clinical characteristics again include dyspnoea, cough, weight loss and weakness. In HRCT, there is a typical finding of GGO; honeycombing is rarely present. The therapeutic success of corticosteroids or azathioprine is greater in more cellular forms of NSIP; the fibrotic subtype has a poorer prognosis with progressive fibrosis, even fatal.

Rare idiopathic interstitial pneumonia

Rare IIPs include **lymphoid interstitial pneumonia (LIP)** and **idiopathic pleuropulmonary fibroelastosis (PPFE)**. **LIP** is characterised by the infiltration of lung tissue with lymphocytes. It can have a connection with pulmonary lymphoma and can be distinguished by using immunohistochemical methods. LIP can also be found in connective tissue disorders,

typically in Sjogren´s syndrome. LIP usually responds well to corticosteroid treatment. **PPFE** is characterised by the thickening of pleura and fibrosis of subpleural interstitium. The prognosis is uncertain.

SARCOIDOSIS

Definition and epidemiology

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology. It is the most common idiopathic ILD, with a prevalence of 1-100 per 100 000 persons. Sarcoidosis commonly affects young and middle-aged adults, more women than men; more patients are non-smokers. There is a variety in the geographical distribution of sarcoidosis; the higher incidence is in regions with a colder climate like Scandinavia, Northern America, or Japan. The disease frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and skin and ocular lesions, but any organ may be affected.

Aetiology and pathogenesis

The cause of sarcoidosis remains uncertain, but there is probably a genetically predisposed abnormal immune reaction to antigen capable of persisting in a tissue. Potential aetiological agents include mycobacteria and *Propionibacterium acnes*. In a pathological immune reaction, all components of the immune system are involved. The typical morphologic unit is epithelioid granuloma, that compartmentalises immune cells leading to their different distribution in the whole immune system, mainly with a significant decrease of CD4+ T-helper lymphocytes. In an active phase of granuloma formation, there is increased activity of lymphocytes and monocytes. Later, activated macrophages, under the influence of Th1 cytokine, morph into giant multinuclear epithelioid cells and Langhans cells containing Schaumann bodies (laminated concretions of calcium and protein) and asteroid bodies (stellate inclusions). The epithelioid granuloma centre is rich in activated CD4+ T-lymphocytes; the periphery includes more CD8+ lymphocytes and fibroblasts. This distribution of lymphocytes is exceptionally typical for sarcoidosis. The ratio of CD4+/CD8+ lymphocytes is decreased significantly in blood but increased over 4 in BAL and serves as a diagnostic tool for sarcoidosis.

Diagnosis

Clinical features:

The clinical presentation of sarcoidosis varies widely. Sarcoidosis may be **asymptomatic**; 30-50% of patients have sarcoidosis discovered on routine chest X-ray for other reasons. The manifested disease symptoms are very nonspecific; they resemble acute or chronic syndrome of system inflammatory response. These include low-grade fever, fatigue, weight loss, night sweats, and arthralgias. Patients may complain of chronic dry cough, dyspnoea, and rarely also chest pain.

Acute sarcoidosis may present as a **Löfgren's syndrome** characterised by fever, bilateral hilar lymphadenopathy, ankle arthritis and erythema nodosum. The ankle tends to be tender, swollen, and pinkish. Erythema nodosum, a skin rash of round red raised nodules is located mostly on the shins and ankles. Respiratory symptoms are infrequent. Sometimes, uveitis and conjunctivitis are present. A rare form of acute sarcoidosis is a sarcoid in a scar.

Chronic sarcoidosis has an insidious onset with organ-related symptoms, such as cough, dyspnoea, and chest pain. Sarcoidosis of the upper airways presents as dyspnoea, sore throat, and dysphonia. Skin lesions include erythema nodosum, lupus pernio, and subcutaneous nodes. In the case of affected eyes, there is pain, photophobia and tearing, and vision may be altered to the point of blindness. There can also be neurological symptoms like headaches, paresthesias, muscular spasms, and even meningitis or encephalitis. Gastrointestinal symptoms include abdominal pain, dysphagia, or jaundice. Nephrocalcinosis, nephrolithiasis or renal failure may occur in affected kidneys. Endocrinological symptoms involve hypercalcemia, hypercalciuria and diabetes insipidus.

Investigations:

The diagnosis is established when clinical and radiographic findings are supported by histological evidence of noncaseating granulomatous inflammation while other causes of granulomas and local reactions have been reasonably excluded. Granulomas themselves are part of various diseases, including tuberculosis, granulomatosis with vasculitis or pneumoconiosis). Diagnostic assessment should provide histological confirmation of disease, assess the extent and severity of organ involvement, assess whether the disease is stable or likely to progress and determine whether the therapy will benefit a patient.

Laboratory findings are not very specific, and we can observe anaemia, leukopenia with lymphopenia, and elevated activity of alkaline phosphatase (ALP). Hypercalcaemia and hypercalciuria result from ectopic production of vitamin D3 in granulomas. Specific biomarkers

are used to assess the activity of the disease, such as an angiotensin-converting enzyme (ACE), neopterin, and the concentration of receptor for IL-2 in the serum (sIL-2R).

The main finding in immunological tests is a decreased ratio of CD4+/CD8+ in peripheral blood. The tuberculin sensitivity test is negative in 70% of patients.

Imaging methods are essential for the diagnosis of sarcoidosis. A **simple chest X-ray** is used for **staging the disease and has a prognostic value**. Stage 0 is a normal finding in patients with extrapulmonary sarcoidosis. **Stage I** refers to bilateral hilar lymphadenopathy. **Stage II** includes both bilateral hilar lymphadenopathy and parenchymal reticular or reticulonodular infiltrates. **Stage III** relates to parenchymal infiltrates without bilateral hilar lymphadenopathy, and **stage IV** reflects signs of fibrosis. **HRCT** provides more details about mediastinal and parenchymal abnormalities; it enables assessing the activity of the diseases. Reversible HRCT patterns include GGO and multiple nodularities, mainly in peribronchial, perilymphatic and subpleural areas. Irreversible HRCT patterns are fibrosis, honeycombing, and distortion of blood vessels and airways. Imaging methods are crucial for picking a biopsy site, e.g., lymphatic node by mediastinoscopy or transbronchial biopsy, pulmonary parenchyma, or more easily accessible skin lesions. Histologic verification is not required for classical Löfgren's syndrome.

Bronchoscopy may reveal hyperaemia of the airways, sometimes yellowish nodularities, and tracheal carina may be distorted by the pressure of hilar lymphatic nodes. BAL in sarcoidosis typically contain 20-40% of lymphocytes; the ratio of CD4+/CD8+ lymphocytes is increased above 4.

Pulmonary function tests reflect the degree of parenchymal involvement; the most sensitive method is diffusion capacity, which decreases as the first parameter. Later, a **restrictive ventilatory impairment** appears. However, sarcoidosis may also affect airways due to distortions by peribronchial or peribronchiolar fibrosis, external compression by lymph nodes, and various mucosal involvement (mucosal inflammation, endobronchial granulomas) leading to stenosis, bronchiectasis, bronchiolitis, even airway hyperreactivity, and occasionally hemoptysis. Thus, an obstructive ventilatory impairment may also be observed, creating combined ventilatory impairment or being limited only in small airways. The presence of fibrosis is typically followed by **hypoxaemia**.

Treatment of sarcoidosis:

The disease course is very variable. In two-thirds of patients, there are **spontaneous remissions**. Adverse prognostic factors include lupus pernio, chronic uveitis, age at onset over

40 years, progressive sarcoidosis, nasal mucosal affection, cystic bone lesions, neural and cardiac sarcoidosis, pulmonary hypertension, and respiratory failure.

The treatment of sarcoidosis depends on several factors, mainly whether the patient is symptomatic. In asymptomatic patients, the method of watch-and-wait might be appropriate. In acute sarcoidosis with Löfgren's syndrome, the treatment is symptomatic, consisting of **nonsteroid antiphlogistics**. Topical therapy can be used for the anterior eye or skin. In symptomatic patients with lung function impairment, systematic **corticosteroids** are the method of choice. In 30-50% of patients, corticotherapy is sufficient to achieve remission. In non-responding cases, an alternative to corticosteroids is ***methotrexate, azathioprine***, and ***hydroxychloroquine***, usually combined with corticosteroids. A novel treatment option in the case of refractory sarcoidosis is the usage of monoclonal antibodies. An inhibition of TNF-α (***infliximab***, ***adalimumab***) and of B-cells (***rituximab***) has been proved to be effective, and other monoclonal antibodies targeting, e.g., IL-1, IL-6 and others are extensively studied, some with promising results. In end-stage sarcoidosis with severe fibrosis, the only option might be lung transplantation.

HYPERSENSITIVE PNEUMONITIS

Hypersensitivity pneumonitis (or **extrinsic allergic alveolitis, EAA**) is an immunologically mediated lung disease in which a hypersensitive response occurs in an individual sensitised to an inhaled antigen. Sensibilisation results from an exposition to organic dust. Frequent antigens are aviary proteins, moulds, bacteria, and low molecular weight chemicals. The disease is often named after a specific occupation:

- **Farmer's lung** – where mouldy hay is the source of antigen – *Micropolyspora faeni, Saccharopolyspora rectivirgula*

- **Bird fancier's lung** – antigens are aviary proteins from feathers or excrements

- **Hot tub lung** – steam and aerosol from hot tubs contain nontuberculous mycobacteria

Pathogenesis involves **precipitating antibodies (precipitins) of class IgG against a specific antigen**. Precipitins can be found in pulmonary parenchyma and blood. The disease is more common in non-smokers, probably due to the immunosuppressant effect of cigarette smoke.

The natural course of the disease may be acute, subacute, or chronic in case of repetitive exposition. **Acute EAA** presents as recurrent dyspnoea episodes, dry cough, oppression on the chest, fever, myalgia, and flu-like syndrome occurring after 4-8 hours after antigen exposure.

Symptoms tend to disappear after 24-48 hours, though they reappear after the next exposure. In **subacute EAA**, there is a slow onset of symptoms, dominated by progressive post-exertion dyspnoea. **Chronic EAA** is a result of untreated subacute form progressing into irreversible fibrotic changes of lung tissue. Fibrosis can naturally induce right heart failure.

Objectively, in all forms of EAA, there are **tachypnoea** and **bilateral basal crepitations**. Clubbed fingers are found in chronic disease. A simple chest X-ray reveals soft **bilateral reticulonodulations** more in the basal parts of the lungs. HRCT patterns vary according to the type of disease. In the acute phase, there are **GGOs**, and in the late stages, bilateral **reticulonodulations to honeycombing**. Pulmonary function tests prove a **reduction of gas diffusion and restrictive ventilatory impairment**. Unlike sarcoidosis, in BAL, there is a decreased ratio of CD4+/CD8+ lymphocytes. Pulmonary **biopsy** should be an option in uncertain diagnosis in a subacute and chronic course; the typical histopathological finding is granulomatous inflammation. A proper and detailed history is crucial for the establishment of the diagnosis of EAA.

The treatment begins with the **absolute cessation of exposure to the provoking antigen**. Corticosteroids are the medication of choice in acute and progressive chronic forms of the disease.

INTERSTITIAL LUNG DISEASE SECONDARY TO SYSTEMIC DISEASE

Collagen tissue diseases

Collagen tissue diseases can trigger pulmonary parenchyma damage, which can be symptomatic and asymptomatic and can have a wide range of clinical traits. Pulmonary involvement in collagen tissue disorders potentially poses a limitation to prognosis and survival. In a patient with ILD, connective tissue diseases should be actively sought.

Rheumatoid arthritis (RA) can affect the respiratory system on several levels. The cricoarytenoid joint may get damaged, leading to hoarseness or stridor. Pleural effusion due to serositis is frequent. It contains a high concentration of protein and rheumatoid factors. Peripheral airways also may be affected, resulting in obliterating or follicular bronchitis. Rheumatoid nodules can exist in many locations of the body, including the lungs. Large cavitating nodules can evolve in the case of concomitant coalworkers' pneumoconiosis (Caplan's syndrome). Histopathological image of affected pulmonary tissue might be of UIP, NSIP, OP and LIP type. Sometimes, it can exacerbate in the form of a picture of DAD. Drugs

used to treat rheumatoid arthritis (e.g., ***methotrexate, leflunomide, infliximab***) may promote inflammatory reactions in the lungs and predispose to lung infections.

Systemic sclerosis (scleroderma, SSc) has frequent pulmonary consequences, mainly in patients with positive autoantibodies against topoisomerase (ATA). Diffuse lung fibrosis is mostly of NSIP type; UIP is rare. The prognosis tends to be rather good. Pulmonary hypertension can develop even without pulmonary fibrosis as a primary vascular phenomenon, seen more in patients with anticentromere autoantibodies (ACA). Disruption in oesophageal motility predisposes a patient to aspiration pneumonia. Constriction of chest movements by contraction of skin is possible but rare.

Systemic lupus erythematosus (SLE) is another systemic disorder where lung fibrosis may occur though it is not frequent. SLE is more often connected to pleural effusions and pleural thickening. Shrinking lungs have been described, possibly because of diaphragmatic myopathy. Opportunistic infections are a recognised risk in an immunosuppressed patient.

Systemic vasculitides

Pulmonary vasculitis is a rare but very dangerous type of pulmonary affection that can be part of systemic vasculitis. The most frequent examples of anti-neutrophil cytoplasmic antibody **vasculitides are granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA)** and **microscopic polyangiitis (MPA)**. Anti-neutrophil cytoplasmic antibodies (ANCA) are often present in systemic vasculitides involving small and medium-sized vessels. ANCAs are categorised as cytoplasmic (c-ANCA, reacting against proteinase 3, typically in GPA), perinuclear (p-ANCA, reacting against myeloperoxidase, typically in EGPA), or atypical.

Vasculitis should be considered in diffuse alveolar haemorrhage, which is suspected in rapid fall of haemoglobin, and unexplained infiltrates on chest imaging. BAL is usually diagnostic of haemorrhage. Also, vasculitis should be presumed in breathlessness on exertion with an unexplained isolated or disproportionate reduction in gas diffusion capacity.

GPA, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis)**,** is characterised by the classic triad of the renal, lower respiratory tract and upper respiratory tract involvement. Chronic rhinitis, sinusitis or mastoiditis may precede generalised disease over months to years. The lower respiratory tract is affected in 65-85% of patients, including diffuse alveolar haemorrhage. Fevers and weight loss are other common symptoms. Histopathologically, we find granulomatous inflammation and necrotising vasculitis of small to medium-sized vessels. Usually, chest imagining displays one or more nodules that

can cavitate, localised or diffuse infiltrates. The positivity of **c-ANCA** is typical, but its absence does not exclude the diagnosis of GPA. The treatment has two phases. The first step is to induce remission of the disease, a combination of **corticosteroids** with ***cyclophosphamide*** is routinely used, sometimes with ***methotrexate*** or ***rituximab*** instead. In severe generalised cases, plasmapheresis may be necessary. The second phase serves to avoid relapses and similarly includes corticosteroids with ***azathioprine***.

EGPA, eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome)**,** requires the achievement of four out of six diagnostic criteria: the presence of **asthma**, peripheral blood **eosinophilia** (> 10%), evidence of a neuropathy in a vasculitic pattern (e.g., mononeuritis multiplex), **transient pulmonary infiltrates**, a history of **sinus disease**, evidence of extravascular eosinophilia on biopsy. Typically, prodrome rhinitis with later development of asthma is followed by eosinophilia in peripheral blood and tissue and, ultimately, systemic vasculitis. Lung biopsy reveals a triad of necrotising angiitis, granulomata and tissue eosinophilia. In two-thirds of the patients, there is the positivity of **p-ANCA**. The treatment is similar to GPA.

PROGRESSIVE FIBROSING PHENOTYPE OF ILDS

We mentioned in the introduction chapter that ILDs share common pathogenetic, clinical, and sometimes radiological and functional characteristics. The one specifically clinically important common behaviour of these diseases is referred to as the „progressive fibrosing phenotype“ of ILDs. A definitive definition is not currently available, but working definitions in the literature include a specific decline of FVC, progression on HRCT, and symptoms over 24 months despite treatment. A typical **prototype of fibrosing ILD is IPF**. Other ILDs that develop a similar clinical course, meaning they are associated with progressive fibrosis, are referred to as having a progressive fibrosing phenotype. From the epidemiological point of view, progressive fibrosing phenotype has been identified in about 25% of patients with fibrosing ILDs other than IPF. ILDs most probable to develop in this course are idiopathic NSIP, unclassifiable idiopathic interstitial pneumonia, ILD associated with rheumatoid arthritis and systemic sclerosis, hypersensitivity pneumonitis, sarcoidosis, and ILDs related to occupational exposures (e.g., asbestosis and silicosis). As some of these diseases are rare, usually, the clinical suspicion falls on IPF first.

The importance of recognizing progressive fibrosing phenotype lies in the subsequent treatment of the disease. While antifibrotic drugs (***nintedanib, pirfenidone***) have been

exclusive for IPF, the treatment of progressive fibrosing ILDs other than IPF usually involves **corticosteroids** or immunosuppressants (e.g., ***azathioprine, mycophenolate mofetil***, and ***cyclophosphamid***e. However, this traditional approach lacks evidence for effectivity; thus, **antifibrotic drugs** already approved for IPF **may also present a game-changer** for other progressive fibrosing ILDs. The use of combination therapy (e.g., antifibrotic and corticosteroid) may improve the treatment of progressive fibrosing ILDs. The precise identification of underlying ILD may often be challenging; therefore, the crucial point is to correctly determine the presence of progressive fibrosis, even as a working diagnosis, to initiate timely treatment.

6 SLEEP AND VENTILATORY DISORDERS

Sleep and ventilatory disorders

- **Sleep apnoea** is a cessation of breathing during sleep lasting at least 10 seconds. **Obstructive sleep apnoea** (OSA) results from a collapse of upper airways with preserved respiratory effort, **central sleep apnoea** (CSA) results from the lack of output from the respiratory centre, **mixed sleep apnoea** (MSA) begins as a central event and continues as obstructive
- Apnoeic event leads to **oxygen desaturation**, **cortical arousal** and **activation of the sympathetic nervous system**, long-term repetition of these reactions results in **chronic intermittent hypoxia**, **sleep fragmentation** and **sympathicotonia** with serious cardiometabolic consequences in morbidity and mortality
- OSA features **snoring**, waking up **choking**, poor quality of sleep, **daytime sleepiness,** and cognitive impairment
- The diagnosis of sleep apnoea relies on **polygraphy** or **polysomnography**
- The basis of the treatment is restoring **patency of upper airways** by behavioural modification, oral appliances, surgery and most importantly, non-invasive application of **positive airway pressure (PAP)**
- **Hypoventilation** is defined as an increase of partial pressure of carbon dioxide measured by blood analysis or nocturnal capnography. It results from a defective respiratory centre or impaired respiratory effectors such as the thorax, respiratory muscles, or lungs
- Due to different regulation of breathing, hypoventilation usually **manifests foremost at sleep**, often accompanied by sleep apnoea
- **Obesity hypoventilation syndrome (OHS)** is defined as obesity combined with **daytime hypercapnia in the absence of any other explanation for hypercapnia**. OSA is present in over 90% of OHS patients. It is an extensively underdiagnosed and undertreated disease.
- The primary route of treating hypoventilation syndromes is the application of **PAP to deepen ventilation and eliminate apnoeic episodes**

SLEEP AND BREATHING

Sleep is a dynamic process involving complex neural activation. The transition between wakefulness and sleep occurs through a process of reciprocal inhibition of clusters of wakefulness-promoting and sleep-promoting neurons. This process works like an absolute switch and prevents intermediate conscious states in a healthy individual.

Cortical electrical activity recorded as an electroencephalogram (EEG) is marked by progressive synchronization. We can recognise different sleep stages due to specific distinct patterns: stages I – III (formerly, even IV) of **Non-rapid eye movement sleep** (NREM) and **rapid eye movement sleep** (REM). These stages revolve in cycles, and one cycle lasts approximately 90 minutes. During one cycle, there is usually progressive deepening of NREM stages followed by REM. These cycles are repeated three to six times per night. They are not uniform; earlier cycles contain more NREM stages, while sleep cycles closer to morning contain more REM sleep. During sleep, muscle tone declines to the point of atony in REM sleep.

Sleep onset is associated with altered chemosensitivity, respiratory drive, and metabolism. It results in changes in lung mechanics and ventilation. With deeper sleep stages, particularly in REM sleep, ventilatory drive decreases. As a result, there is a decrease in tidal volume, alveolar ventilation, and blood gases. There is an increase in $PaCO_2$ and proportional reduction in PaO_2 compared to wakefulness. Ventilatory response to hypercapnia and hypoxia is also blunted. While in healthy individuals, these changes carry no risks, in patients with one or more pre-existing disorders, they may precipitate further disruption of ventilation and lead to pathological changes of blood gases with harmful consequences.

DEFINITION AND CLASSIFICATION

The latest instalment of the International classification of sleep disorders (ICSD) from the year 2014 recognises several categories of sleep disorders: insomnia, sleep-related breathing disorders (SRBDs), central disorders of hypersomnolence, circadian rhythm disorders, parasomnias, sleep-related movement disorders, and other. While most of these are the domain of neurology, SRBDs are linked to respiratory control. SRBDs contain a wide variety of syndromes (see Table 6.1.).

Table 6.1. Classification of sleep-related breathing disorders

Obstructive sleep apnoea syndromes
Adult
Paediatric
Central sleep apnoea syndromes
Central sleep apnoea with Cheyne-Stokes breathing
Central sleep apnoea due to a medical disorder without Cheyne-Stokes breathing
Central sleep apnoea due to high altitude periodic breathing
Central sleep apnoea due to a medication or substance
Primary central sleep apnoea
Primary central sleep apnoea of infancy
Primary central sleep apnoea of prematurity
Treatment-emergent central sleep apnoea
Sleep-related hypoventilation disorders
Obesity hypoventilation syndrome
Congenital central alveolar hypoventilation syndrome
Late-onset central hypoventilation syndrome with hypothalamic dysfunction
Idiopathic central alveolar hypoventilation
Sleep-related hypoventilation due to a medication or substance
Sleep-related hypoventilation due to a medical disorder
Sleep-related hypoxemia disorder
Isolated symptoms and normal variants
Snoring
Catathrenia

The most common presentation of these disorders is sleep apnoea. Sleep **apnoea** is defined as the cessation of airflow in the upper airways during sleep for at least 10 seconds. While apnoea means a complete stopping of the airflow, **hypopnoea** is the term expressing a partial limitation of airflow, i.e., reducing airflow under 50%.

Two main pathophysiological mechanisms leading to an apnoea are obstruction in the upper airways and halt in the respiratory drive.

The former is the cause of **obstructive sleep apnoea (OSA)**. In OSA, the respiratory drive keeps stimulating breathing muscles. Consequently, respiratory effort, i.e., movement of the thorax and abdomen, is preserved. However, in **central sleep apnoea (CSA)**, the

respiratory centre does not sustain the respiratory effort for various reasons. The combination of the two is **mixed sleep apnoea (MSA)**. The respiratory centre initially gives no impulse for inspiration and later resumes its activity; hence the respiratory effort is absent in the first part of the episode and later is present. An example is illustrated in Figure 6.1. The most common type of apnoea is OSA (about 80%). CSA and MSA each occur in about 10% of cases.

A common consequence of all types of apnoeas is decreased oxygen saturation called **desaturation** (a drop of at least 3%). Desaturation and other reflex mechanisms lead to activation of the cortex called **arousal**, which usually terminates apnoeic/hypopnoeic episode.

Hypoventilation is characterized by the increased partial pressure of carbon dioxide recorded either utilizing capnography or by blood gases analysis. It is always associated with hypoxemia. However, hypoxemia does not need to be accompanied by hypercapnia.

OBSTRUCTIVE SLEEP APNOEA

Epidemiology

OSA is the most common type of SRBD. There are numerous epidemiological studies that attempted to establish the prevalence of OSA. Nonetheless, since they differed in the methodology, it is somewhat challenging to compare their results.

Most literature states the prevalence of clinically significant OSA (i.e., recommended for treatment) to be 4% in men and 2% in women. In comparison, the mild degree is present in almost 24% of men and 9% of women in the general population. Newer studies, however, document an increase in the prevalence of clinically significant OSA to **13% in men and 6% in women**, which constitutes an increase of 14-55% over 20 years. This enormous increase is generally attributed to the obesity pandemic.

A serious issue in diagnostics of OSA is the difference between men and women. Historically, it was speculated that men are ten times more likely to be affected, but the ratio of men to women suffering from OSA is about 2-3 to 1. While male sex is a significant risk factor for OSA, women are often severely underdiagnosed. They either are reluctant to admit to snoring, or their practitioner omits the possibility.

Aetiology and pathogenesis

Risk factors for OSA are those that promote upper airway collapsibility. Generally, they are age, male sex, obesity, craniofacial deformities, and genetic factors.

The higher risk in **men** lies in having disproportionately smaller airways, predominately abdominal type of obesity. Also, in women, there are hormones with a protective

effect against OSA before menopause. After menopause, the proportion of affected men and women evens out.

OSA evolves with **age**, and it usually becomes more clinically significant later in life, usually in middle age. The prevalence of OSA in elderly individuals tends to go down, and these patients curiously suffer from a less debilitating clinical picture.

Obesity is a significant factor for OSA, mainly visceral obesity or abdominal obesity. Around 70% of people with a body mass index (BMI) $\geq$ 40 kg/m^2 have OSA. An increase in a person's weight of 10% increases the chance of developing OSA six-fold. Abdominal fat impairs ventilatory mechanics, and it is associated with depositing fat in the neck not only around the upper airways but also inside the airway walls. Patients with OSA tend to have a generally thicker neck. **Circumference of the neck** below 37 cm is associated with a significantly smaller OSA risk, while a neck circumference of more than 48 cm is related to a higher risk of OSA.

As upper airway morphology is partially hereditary, OSA tends to run in the family. Every **direct relative suffering from OSA** increases the risk of the disease.

Anatomic anomalies of the face and neck are strongly linked to OSA. Skeletal deviations include, e.g., maxillary or mandibular hypoplasia, retroposition, and hyoid position. Endocrine diseases (acromegaly, hypothyroidism) can lead to an enlarged tongue or other soft tissues. Adenotonsillar hypertrophy appears to play a role in OSA, mainly in children. These anatomical alterations are parts of congenital syndromes like Pierre-Robin syndrome, Morbus Crouzon, or Down syndrome. Functional abnormalities, like increased pharyngeal compliance, impaired reflexes, or changes in the ventilatory drive, also seem to induce apnoeic episodes.

The primary **mechanism of OSA is a repetitive partial or complete collapse of upper airways on the level of the pharynx during sleep**. This collapse occurs mostly at the end of expiration or the peak of inspiration. The place of collapse is retropalatal and retroglossal, and it continues caudally. The collapse is the most pronounced during REM sleep because of skeletal muscle atony. At the onset of sleep, the muscle tone of the pharynx is reduced in healthy individuals, but the airways stay patent. In OSA patients, there are anatomical and functional changes in the pharyngeal muscles. These muscles are more active during wakefulness, probably because they must compensate for the increased resistance from the fat tissue. It is like training the skeletal muscle in a work-out. However, during sleep, the reflex activity is reduced or absent, which leads to partial or complete closure of the airway.

The smallest degree of closure changes the airflow from laminar to turbulent, reverberating soft tissues and producing the acoustic phenomenon of snoring.

More airway closure impairs gas exchange between alveolar and ambient air. It means that there is sudden and rapidly progressing hypoxia and hypercapnia. It registers on pulse oximetry as **oxygen desaturation**. Simultaneously, there are still impulses coming to inspiratory muscles forcing the body to breathe. Inspirational activity against closed airways deepens **negative intrathoracic pressure,** and that has far reached hemodynamic consequences. Hypoxia and hypercapnia are stimulating for the respiratory centre, which leads to **arousal**, which can be demonstrated on EEG as the change of cortical activity. It can be likened to the sudden transition from deeper sleep to more shallow lasting several seconds. The activation of the cortex leads to increased general skeletal muscle tone, including muscle tone in the pharynx and the airways are suddenly opened. Often, this is accompanied by a loud snoring sound. Usually, the patient does not notice the arousal. Sometimes though, the arousal leads to full awakening, and the patient can sense how his closed throat is opening, or he can hear himself snore.

The hypoxia, arousal, and deepening of the negative intrathoracic pressure activate the sympathetic nervous system through various pathways leading to other effects, like heart rate changes or increased blood pressure.

Diagnosis

Clinical features:

Symptoms can be very variable. Early stages of OSA may be completely unnoticed by the patient, which presents a risk for future complications. While some symptoms are sensed directly by the patient, it is often **a report from a bed partner** that is crucial for setting the diagnosis.

Symptoms are classified into night-time symptoms and day-time symptoms.

The most revealing symptom is waking from sleep **choking** or the sound of their own snoring. The patients also report **frequent awakenings**, often nycturia several times per night. As they usually sleep with an open mouth, partially as an attempt to compensate for lack of air, they complain of **parched mouth**. The patients report they have a glass of water on the nightstand. On the contrary, some patients complain about saliva leaking out of their mouth. Sympathetic activation leads to profuse sweating, mostly on the chest, neck and back of the head. Also, when awoken, they can have heart palpitations. Intense inspiratory effort precipitates gastroesophageal reflux so that the patient can complain of heartburn.

Objectively, the bedpartner observes **snoring** and **stops in breathing**. Snoring should raise suspicion when it is very loud, present in every position, not only on the back, when it is

ragged and not regular, and of course when it wakes the patient. The presence of observed apnoeas is practically pathognomic for OSA. Though, it does not inform about its severity.

OSA can often be accompanied by other sleep disorders, frequently by periodic limb movements or sleep-related behaviour disorders. As a result, there is a higher likelihood of bruxism, sleep-talking and sleepwalking.

Most patients have no problem falling asleep, as they tend to be very tired. A minority, mostly women, may complain of insomnia.

In the morning, the patient complains of **not refreshing sleep**, and he usually feels as though he has not slept enough and needs more sleep or reports that the patient is more tired in the morning than in the evening. They often have a dry throat, and they drink first thing in the morning. **Morning headache** is very typical, a result of not only lacking sleep but of sustained nocturnal hypercapnia. The most common daytime symptom is **sleepiness**. It should be distinguished from tiredness which occurs when one is physically or mentally exhausted. Sleepiness can be relatively inconspicuous, present only when the individual is bored or inactive. It can also be dire, like when the patient is falling asleep while talking to someone. To some extent, it can be compensated for, but sleepiness is a hazardous sign, mostly when the patient's profession includes driving or working at heights. OSA increases the risk of traffic collisions two 2,5-3 folds.

Long-term nonrestorative sleep has consequences on **mental performance**. They include depression, long-term memory, executive functions like analysis, synthesis, contextual memory, and working memory. The real-life difficulties patients must face are maintaining motivation, rigid thinking, and emotional lability.

Detailed sleep history includes questions about snoring, waking up choking, observed apnoeic episodes, total sleep time, sleep latency, sleep fragmentation, nycturia, insomnia, daytime sleepiness, and problems with memory, concentration, or mood. It is essential to clarify the sleep pattern as it can be a possible source of daytime sleepiness. Even if the bed partner is not present in the office, we inquire whether he noticed any OSA signs. Also, we should not forget to ask about weight changes. Often, in retrospect patient relays that the beginning of his symptoms overlaps with a progressive weight increase. As OSA demonstrates some hereditary traits, we should inquire about family history.

It is vital to assess the conditions secondary to potential OSA, such as cardiovascular and metabolic morbidity.

Investigations:

In **physical examination,** we concentrate on frequent clinical characteristics of OSA: male sex, postmenopausal age in females, obesity (notably central), and upper airway anatomy abnormalities like retrognathia, retrogenia, and microgenia. It is recommended to measure the neck, abdomen, and hip circumference and specify BMI and Mallampati score. Mallampati score is a tool used in anaesthesiology, semi-quantifying the space in the throat to grade orotracheal intubation risk.

Several **scoring tools** help in establishing the probability of OSA, usually used in screening. For evaluating sleepiness, the **Epworth sleepiness scale and Stanford sleepiness scale** are used. For example, the Epworth sleepiness scale computes the degree of daytime sleepiness by appointing points to eight real-life situations according to the chance of falling asleep in these situations.

The **overall probability of OSA** is screened by the Berlin questionnaire, STOP and STOP-Bang questionnaires. Berlin questionnaire classifies patients into low-risk and high-risk groups according to snoring, daytime sleepiness, presence of obesity and hypertension. Similarly, the STOP questionnaire assesses snoring, observed apnoeic episodes, daytime sleepiness, and hypertension. Two positive answers put a patient into the high-risk group. STOP-Bang adds entries about age, sex, BMI, and neck circumference, which brings its sensitivity up to 87%.

If the clinical suspicion for OSA is established, objective monitoring is recommended. There are three levels of objective monitoring.

The first one is **pulse oximetry**, which records the number of desaturations. Desaturations are the direct consequence of apnoeic/hypopnoeic episodes. It is used in office settings as a screening tool.

Cardiorespiratory polygraphy (PG) expands pulse oximetry by recording oronasal/nasal airflow, respiratory effort, snoring and sleep position. This method is advantageous in patients with OSA of a severe degree. In some countries, it is validated to be the basis for the prescription of therapy. However, in mild or moderate OSA, its precision decreases as it does not record sleep stages.

The golden standard of sleep studies is **complete overnight polysomnography** (PSG). To the previously mentioned channels, it adds recording of electroencephalography (EEG), electrooculography (EOG), electromyography (EMG) of mental and anterior tibial muscles, electrocardiography (ECG), and video monitoring. For research purposes, an oesophageal

pressure sensor may be inserted. An example of a polysomnographic recording can be seen in Figure 6.1.

In the beginning, we have established basic definitions of each respiratory event. PG and PSG allow for evaluation of these events with precision and grade the type and severity of the finding. **Apnoeic-hypopnoeic index** (AHI) is the main indice used to stratify the severity of the problem; it is a mean number of apnoeic and hypopnoeic episodes per hour of sleep.

Oxygen desaturation index (ODI) is the number of desaturations per hour of sleep. It expresses a degree of chronic intermittent hypoxia (CIH). Other parameters such as mean saturation, minimal saturation, or time spent below saturation of 90% are also considered. They enable us to predict the probability of hypoventilation, notably in obese patients with many comorbidities. **Arousal index**, the number of arousals per hour, represents sleep fragmentation. Distinct sleep stages are scored to establish a hypnogram (succession of sleep stages in 30-second-long epochs); this allows us to understand if there is deprivation of deep sleep stages like NREM III or REM. Sleep scoring is only possible in PSG; that is why it is a golden standard. Also, PSG is usually conducted under a sleep technician's supervision, ensuring the better technical quality of the acquisition.

As mentioned, AHI is the parameter that categorizes the **severity of sleep apnoea**. AHI below 5 episodes/hour is physiological. AHI 5-15 episodes/hour indicates mild sleep apnoea, AHI 15-30 episodes/hour moderate sleep apnoea and AHI over 30 episodes/hour for severe sleep apnoea. This classification applies to all types of apnoea, not only obstructive.

At this point, we must stress that the term OSA in the strict sense, describes the characteristic of a single event or overall PG/PSG finding. The diagnosis itself should be referred to as obstructive sleep apnoea syndrome (OSAS) as it also includes a subjective component of the patient's symptoms. However, in this publication, we use the term OSA also for the diagnosis to avoid confusion.

Consequences and complications

The obstructive apnoeic event triggers immediate desaturation, decreased negative intrathoracic pressure and cortical arousal. Desaturation, intrathoracic pressure swing and arousal activate the sympathetic nervous system by various reflex mechanisms. That, in turn, leads to acute haemodynamic changes, like blood pressure increase (up to 230/170 mmHg) and changes in heart rate. Frequent activation of the sympathetic nervous system results in a chronic state of **persistent sympathicotonia**. Persistent alteration in the autonomic nervous system has been linked to **chronic subclinical inflammation** that is a factor in many cardiovascular and

metabolic diseases. This general inflammation might be further supported by repetitive desaturations or **chronic intermittent hypoxia** (CIH) that promotes oxidative stress. Sympathicotonia, oxidative stress and chronic inflammation are very harmful to the endotel, and **endothelial dysfunction** is thought to be the starting point of atherosclerosis and cardiovascular diseases.

Moreover, the endotel may be mechanically damaged by repetitive surges of blood pressure. The transmural pressure, i.e., the difference between intrathoracic and intraventricular pressure, endures rapid changes that strain the walls of the heart chambers and magistral blood vessels. Neurohumoral factors like oxidative stress and chronic inflammation further damage insulin and leptin metabolism, preventing the patient from losing weight. These processes are very complex, interlinked and form a vicious cycle.

The patient with OSA does not notice these changes until they present in the clinical form of cardiovascular or metabolic disease.

Arterial hypertension is present in 35-80% of patients with OSA, and conversely, around 40% of patients with hypertension have recognised or unrecognised OSA. In OSA, night surges of blood pressure do not allow the blood pressure to drop physiologically. It is called a "non-dipping" pattern, sometimes even "reverse dipping", that is, blood pressure at night is higher than during the day. OSA is a recognised trigger of secondary hypertension. Also, in OSA patients, arterial hypertension can be complicated to treat. When a combination of at least three antihypertensives, including a diuretic, does not lead to target blood pressure values is called resistant hypertension. OSA is the leading cause of resistant hypertension.

Similarly, OSA patients have an increased risk of heart failure, arrhythmias, coronary artery disease, myocardial infarction, sudden cardiac death, stroke, dyslipidaemia, and diabetes. OSA is a frequent part of metabolic syndrome. In fact, in patients with these diseases, the probability of OSA should always be established.

Conversely, when OSA is diagnosed, it is imperative to actively seek undiagnosed hypertension and assess the left ventricular diastolic function by echocardiography and overall cardiovascular risk (obesity, lipid, and glucose metabolism).

Treatment of OSA

OSA treatment aims to maintain the patency of the upper airways. The strategy to do so depends on the severity of the disease and the patient’s preference.

Lifestyle modifications are recommended for all patients to alleviate the severity of the disease, although they may be sufficiently effective in milder degrees of OSA. Weight loss of

10% has been related to a decrease of AHI by 26%. For some patients, bariatric surgery can be considered. Sleeping position can also affect the severity of the disease. Generally, the severity of OSA is the worst in the supine position. In some patients, there is also a specific phenotype POSA (positional OSA), where a substantial majority of respiratory episodes occur in the supine position; nevertheless, so far, there is no widely accepted definition, and the prevalence of this phenotype is unknown. For these patients, a sleep position device is available. It takes the form of a strap around the chest that vibrates when the patient turns onto the back. Avoidance of any myorelaxants is recommended to prevent the further relaxation of upper airway muscles. They include alcohol, sedatives, and hypnotics. Abstinence from smoking is also recommended, although how exactly smoking might influence the severity of OSA is yet to be elucidated. Upper airway inflammation and altered neuromuscular function, arousals and disturbance in sleep architecture have been considered.

Another treatment modality uses **oral devices** that protract the tongue or mandible to the front and increases retroglossal space. This method is useful in mild OSA and is recommended in POSA, mostly in younger and slimmer patients.

There are also several **surgical procedures** aiming to dilate the upper airways. These are also recommended for patients with mild OSA and moderate-to-severe OSA where other options have failed. Results of upper airway surgery are often underwhelming. That is why it is advisable to try to identify the site of obstruction before surgery. For this reason, a method called DISE (drug-induced sleep endoscopy) has been developed. The possible surgical procedures include tonsillectomy (in this indication, mostly successful in children), correction of nose patency, uvulopalatopharyngoplasty (UPPP) or glossectomy. Sometimes, multilevel surgery is needed to address several airway segments. In patients with skeletal deformities, extensive plastic surgery may be needed, like maxillo-mandibular advancement. Historically and in emergencies, the ultimate resolution of sleep apnoea has been tracheostomy.

The golden standard of moderate to severe OSA is the non-invasive use of **positive airway pressure (PAP)**, either as **CPAP (continuous positive airway pressure) or BiPAP (bilevel positive airway pressure)**. The principle is the pressure of air generated by the machine administered to the patient through the hose and nasal or oronasal mask. The pressure of the air acts as a mechanical splint that prevents the collapse of the airways. It is a method of choice to treat OSA. As the patient exhales against this pressure, there can be some initial discomfort. In CPAP, the air pressure provided by the machine is constant during the whole breathing cycle. Usually, personalised pressure is set for the patient, and the mask is carefully chosen to maximise the patient's comfort. BiPAP machines produce higher inspiratory pressure

(IPAP) and lower expiratory pressure (EPAP). Lower expiratory pressure helps to acquiesce more quickly to the PAP treatment; hence this method is chosen when a patient cannot tolerate CPAP. At the same time, the difference between IPAP and EPAP deepens the patient's ventilation. That is the basic principle used in patients with hypoventilation related to, e.g., COPD, obesity hypoventilation syndrome or neuromuscular diseases.

Pharmaceutical agents have been researched, mainly drugs used in other conditions as antidepressants, diuretic ***acetazolamide***, ***theophylline*** or ***modafinil,*** mainly used to treat CSA, but none has been able to reduce the severity of the condition by more than 50%.

OSA and other respiratory comorbidities

OSA is a very prevalent condition. It can coexist with other respiratory diseases, e.g., COPD, pulmonary fibrosis, obesity hypoventilation syndrome. The combination of the two conditions worsens the prognosis for both.

A typical example of such a situation is a combination of OSA and COPD, known as overlap syndrome. Obstruction for the airflow exists on multiple levels. In COPD, there is dynamic compression of the lower airways that impairs expiration. In OSA, there is a repetitive collapse of the upper airways. Consequently, severe hypoxemia may persist even in inter-apnoeic periods, while in simple OSA without COPD, oxygen saturation after apnoea usually reaches a physiological level.

There is an increased risk for developing chronic respiratory insufficiency, right heart failure, arrhythmias, and increased mortality in OSA-COPD overlap syndrome. Other respiratory comorbidities should be actively sought in patients with OSA, and procedures like spirometry and blood gas analysis should be part of routine diagnostic management.

CENTRAL SLEEP APNOEA

Definition

CSA is defined by the recurrent cessation of airflow and simultaneous reduction of breathing effort. Ventilatory impulses generated by the brain stem are lacking in CSA. It is estimated that 10% of breathing disturbances during sleep are of central origin. Pathophysiologically, we recognise two groups of CSA, hypercapnic and non-hypercapnic.

Aetiology and pathogenesis

Hypercapnic central sleep apnoea:

Disorders of the respiratory centre entrail both short and long halts in respiration. Short pauses of respiration are CSAs. Long-lasting diminished breathing is hypoventilation. Hypoventilation occurs not only during sleep but also during the day. The respiratory centre is unable to react to the increase of $PaCO_2$ by increasing activity. A typical example of hypercapnic CSA is **congenital central hypoventilation syndrome**, also known as Ondine's curse. It is a genetic condition caused by a mutation of the PHOX2B gene, regulating the differentiation of neurons, especially in the autonomic nervous system. The mutation results in the incapacity of the respiratory centre to increase ventilation when needed. Typical clinical presentation includes hypoventilation upon falling asleep in infants. Sometimes, it manifests in adulthood as an acute respiratory failure due to inadequate compensatory increase of ventilatory effort in respiratory infection. It is often accompanied by difficulties in regulating blood pressure, heart rate in response to physical effort, low body temperature or sweating.

A secondary cause of respiratory centre dysfunction is most commonly **stroke**. Some **medications** can also stifle respiratory drive, such as opioids or hypnotics.

Non-hypercapnic central sleep apnoea:

Non-hypercapnic CSA occurs because of chronic instability of breathing regulation. This instability presents as short-termed hyperventilation that depends on the overshooting of the ventilation, apnoeic threshold changes, and increased chemosensitivity. Levels of $PaCO_2$ are normal or slightly decreased. Further decrease of $PaCO_2$ positions $PaCO_2$ below the apnoeic threshold, i.e., $PaCO_2$ is insufficient to stimulate the brain stem.

Several situations reduce the sensitivity of the respiratory centre. Primary or idiopathic CSA has no recognised cause. High-altitude CSA is short-termed and alleviates by descending

to a lower altitude. The clinically most significant situation is central apnoea associated with Cheyne-Stokes respiration (CSR).

Central sleep apnoea with Cheyne-Stokes respiration (CSA-CSR):

Cheyne-Stokes respiration (CSR) can be considered a subgroup of CSA. The most relevant risk factors for this condition are cardiovascular diseases, such as heart failure, stroke, and atrial fibrillation.

During wakefulness, ventilation is primarily regulated by behavioural factors. However, during sleep, it is mainly influenced by metabolism, that is, by the production and elimination of CO_2. An increase of $PaCO_2$ (hypercapnia) stimulates ventilation, and a decrease of $PaCO_2$ (hypocapnia) reduces ventilation. Moreover, in contrast, the level of $PaCO_2$ is influenced by any disturbance of respiration, e.g., by cortical impulses, pain, and stress.

The critical elements in ventilatory regulation are chemoreceptors, apnoeic threshold and central ventilatory drive. Central and peripheral chemoreceptors in the ventilatory system measure level of $PaCO_2$ and constitute a feedback gain. In patients with CSA, **chemoreceptors**, mostly peripheral, are prone to hyperreactivity. The **apnoeic threshold** is a level of $PaCO_2$ below which breathing ceases. During normal breathing, $PaCO_2$ is consistently kept above the apnoeic threshold, but in patients with CSA, it has been shown to be elevated. Thus, the risk of $PaCO_2$ dropping below the threshold is more significant.

The **central ventilatory drive in CSA is unstable**. It is activated by chemical irritation of the pulmonary tissue receptors. In patients with heart failure, this irritation is caused by pulmonary congestion. Circulatory delay in heart failure influences the perception of $PaCO_2$ variations. A strong response to breathing disturbances is known as high loop gain and results in overshooting or undershooting ventilation. **Cycles of overshooting and undershooting ventilation** give the impression of crescendo-decrescendo oscillations of tidal volume and respiratory frequency characterising CSR. In CSR, a drop of $PaCO_2$ below the apnoeic threshold initiates an episode of central apnoea, and then the level of $PaCO_2$ increases, which stimulates the respiratory centre. The respiratory centre overshoots its response, causing hyperventilation, leading again to a reduction of $PaCO_2$ (see Figure 6.2.).

The cycle of apnoea-hyperventilation can last 30-50 seconds, even longer, in more severe conditions. In contrast to OSA, arousal is not needed to activate breathing. However, arousal still occurs to some degree. Unlike in OSA, even though there are clear oxygen desaturations, the average saturation may still be in a normal range. However, in patients with CSA-CRS, the presence of obstructive episodes is also common. OSA promotes left heart

failure directly by increasing strain on the heart and large blood vessels and indirectly by other cardiovascular consequences (endothelial dysfunction, atherosclerosis, arterial hypertension, various arrhythmias). The OSA is facilitated by rostral fluid shift, thus thickening the soft tissues of the upper airways. The distribution of obstructive and central episodes varies from night to night and even during a single night, with more obstructive episodes in earlier hours of sleep and more central episodes later in the night.

Clinical features

Patients with CSA-CSR may present with symptoms of both heart failure and sleep apnoea. They report daytime sleepiness, low tolerance of physical effort and nocturnal dyspnoea. Sometimes, however, the daytime symptoms, such as daytime sleepiness, are not noticed due to overwhelming symptoms of the underlying disease. Patients with heart failure are usually elderly, and their sleep is more disturbed compared to younger patients. Similarly, heart failure itself, other conditions and older age also impair sleep subjectively and objectively. Unlike in OSA, a clear causal association between CSA and neurobehavioral sequelae cannot be established.

In OSA, cardiovascular disorders are usually the consequence of the disease, while in CSA, they are usually the cause, the principal one being chronic heart failure.

Oscillations of heart rate, oxygen saturation, and ventilation are distinctly different from obstructive episodes with negative intrathoracic pressure swings and consecutive hypoxia. Obstructive episodes can be incredibly detrimental to the failing heart with either systolic dysfunction (reduced ejection fraction) or diastolic dysfunction (increased filling pressures). Such a heart is more vulnerable to increased blood pressure or sudden activation of the sympathetic nervous system.

Evaluating the cardiovascular consequences of CSA is difficult, and uncertainty remains whether CSA contributes to morbidity and mortality in patients with heart failure or whether CSA is merely an epiphenomenon. Nevertheless, some studies indicate that CSA in patients with cardiovascular disorders, stroke, and renal failure have been associated with significantly reduced survival.

Treatment of CSA

The therapeutic approach to CSA associated with hyperventilation begins with optimal **treatment of an underlying disease**, i.e., pharmacological or interventional cardiac or cerebral options. Everyday substances like ACE inhibitors and beta-blockers have been shown to

improve cardiac function and slightly reduce the number of central sleep episodes; similar outcomes were observed in patients with severe left ventricular systolic dysfunction by using bi-ventricular pacemakers.

As for the treatment of CSA itself, the use of oxygen has been considered. The intended mechanism of use is improved left ventricular function and reduced reflex activation of the peripheral chemoreceptors. Nonetheless, the effect on AHI and clinical symptoms has not been sufficient. Therefore, its routine use is not recommended.

Pharmacological **agents stimulating the respiratory centre** like acetazolamide and theophylline have also been studied. Despite having the benefit of reducing central disturbances by half, concerns have been raised that promoting hyperventilation may worsen the loop gain, and these stimulants are not widely recommended.

In recent years, **PAP** has been a routinely used strategy. PAP keeps the patency of upper airways, abolishes OSA, and improves ventilation/perfusion mismatch in the lungs. PAP may also reduce venous return to the heart and, consequently, cardiac output. It decreases pressure swings and consequently left ventricular afterload in heart failure. Finally, PAP alleviates work of breathing, oxygen consumption of the respiratory muscles and consequently heart function. Although CPAP tends to reduce AHI by about 50%, it does not normalise respiration. In some cases, CPAP has an effect on AHI after prolonged use (usually, at least three months). CPAP is partially effective on AHI, oxygen saturation and left ventricular function, but its effect on survival has not been consistently confirmed.

A novel method of applying PAP called **adaptive servo-ventilation** (ASV), similar to BiPAP, has been put into practice. This setting compensates for overshooting and undershooting of ventilation by automatically adapting pressure. ASV has been shown to be superior to PAP in the reduction of AHI and stabilisation of breathing. Nonetheless, data on survival have been uncertain, and namely, in patients with reduced systolic function, its use was discontinued.

PAP, mostly BiPAP, is a treatment of choice for hypercapnic CSA associated with hypoventilation due to insufficient ventilatory drive or due to neuromuscular or thoracoskeletal disorder is non-invasive ventilation. Long-term oxygen therapy is added in case of persistent hypoxemia despite the normalisation of minute ventilation.

Patients with primary CSA should be treated if they suffer from clinical symptoms, cognitive impairment or daytime sleepiness.

SLEEP-RELATED HYPOVENTILATION

During sleep, the alveolar ventilation is physiologically decreased, and ventilatory response to hypoxemia and hypercapnia is weakened, mostly during REM sleep with dysrhythmic breathing. It is less reduced during NREM sleep. In healthy individuals, this poses no risk, but in patients with pre-existing respiratory diseases or conditions, nocturnal hypoventilation develops that usually precedes the daytime manifestation of respiratory failure.

Sleep-induced hypoventilation is characterised by elevated levels of $PaCO_2$ over 6,0 kPa (45 mmHg) while sleep or disproportionately increased relative to levels during wakefulness.

The conditions associated with nocturnal hypoventilation are summarised in Table 6.2.

Table 6.2. Disorders associated with nocturnal hypoventilation

Neuromuscular disorders
Stable or slowly progressive
▪ Previous poliomyelitis ▪ High spinal cord injury ▪ Spinal muscular atrophy ▪ Congenital myopathy
Rapidly progressive
▪ Motor neuron disease (i.e., amyotrophic lateral sclerosis, ALS)
Chest wall abnormalities
▪ Kyphoscoliosis ▪ Post tuberculosis sequelae ▪ Thoracoplasty ▪ Obesity hypoventilation syndrome
Lung disorders
▪ Chronic obstructive pulmonary diseases ▪ Cystic fibrosis ▪ Overlap syndrome (lung disease with obstructive sleep apnoea)
Ventilatory control abnormalities
▪ Brainstem injuries: stroke, infection, tumour ▪ Congenital central hypoventilation ▪ Primary alveolar hypoventilation

In conditions where the lungs are abnormal or damaged (COPD, cystic fibrosis, tuberculous sequelae), hypercapnia may be mainly the result of worsening lung mechanics and ventilation-perfusion inequalities. In most mentioned conditions, there is pump failure with a decreased ventilatory drive. Sustained hypercapnia invokes compensatory renal mechanisms, namely retention of bicarbonates HCO_3^-. An increased concentration of HCO_3^- in blood translates to increased concentration in cerebrospinal fluid. Increasing pH in cerebrospinal fluid

hinders the response of the ventilatory centre to hypercapnia. Therefore, it further promotes hypoventilation, consequently forming a vicious cycle. Hypercapnia is seldom isolated; it usually coexists with hypoxemia. In hypoventilation, oxygen in alveoli is displaced by the increased partial pressure of carbon dioxide. The lower partial pressure of oxygen in alveoli decreases the alveolar-capillary gradient, and diffusion of oxygen towards capillary decreases as well.

OBESITY HYPOVENTILATION SYNDROME

Definition and epidemiology

Obesity hypoventilation syndrome (OHS), formerly known also as Pickwickian syndrome, is defined by the presence of **obesity** (BMI > 30 kg/m^2), **daytime hypercapnia** ($PaCO_2$ > 6,0 kPa or 45 mmHg) in the **absence of another cause of said hypercapnia**. It is the most severe consequence of obesity-induced breathing disorder. OHS is associated with higher mortality and cardiovascular morbidity (congestive heart failure, pulmonary hypertension). Its prevalence has been growing in recent years, probably due to the obesity pandemic. In Europe, almost 16% of the general population is obese, with a BMI of over 30 kg/m^2. The estimate for OHS prevalence in the general population is thought to be 0,15-0,3%. In obese patients referred to pulmonology specialist, it increases by about 0,5-2,3%. Perhaps surprisingly, about half of patients with a BMI over 50 kg/m^2 suffer from OHS.

OHS has a robust association with OSA. Among patients with OSA, 20-30% also suffer from OHS. Conversely, OSA is present in 90% of OHS patients, and approximately 70% of OHS patients have OSA of a severe degree. Unlike OSA, women seem to be affected more frequently than men.

Aetiology and pathogenesis

Not every obese patient also suffers from hypoventilation. The pathogenesis of OHS is very complex, and more than one mechanism plays a role. Firstly, in obesity, the **mass of the abdomen hinders caudal traction of the lungs in inspiration**. Chest wall thickness is increased. Altogether these factors reduce the compliance of the respiratory system. The respiratory muscles must increase their load of work to overcome the increased elastic resistance of the respiratory system. This leads to their eventual exhaustion. Pulmonary volumes and capacities decrease. Primarily, there is a reduction of tidal volume and inspiratory and expiratory reserve volume. On the other hand, functional residual capacity increases, similarly

to patients with COPD and hyperinflation. Basal parts of the lungs tend to be less effectively ventilated, leading to ventilation/perfusion mismatch.

Secondly, **obesity triggers metabolic changes**. The increased body mass produces carbon dioxide in larger quantities than in normal-sized individuals. Also, lipid tissue is a source of pro-inflammatory cytokines, and it generates chronic subclinical systemic inflammation. Another molecule produced in lipid tissue is leptin, a hormone of satiety. In obese individuals and further in patients with OSA, leptin resistance occurs, which causes the overproduction of leptin. Leptin resistance is part of the reason why obese individuals have problems losing weight. Besides, leptin resistance reduces the ventilatory response of the respiratory centre to stimuli. The ventilatory response is further blunted by an increased level of bicarbonates, as discussed previously.

Lastly, **OSA impairs ventilatory mechanics** by obstructing airways and causes nocturnal intermittent hypoxia and hypercapnia independently from previous mechanisms. Hypoxia impairs the regular production of neurotransmitters. Natural arousal reaction in OSA is inadequate, abolishing usual inter-apnoeic hyperventilation that eliminates carbon dioxide accumulated in previous apnoea.

Diagnosis and differentional diagnosis

Clinical features:

The typical triad of clinical presentation in OHS is obesity, sleepiness, and central cyanosis. Chronic hypoxemia often causes polyglobulia that favours cyanosis. The patients complain of dyspnoea and a low tolerance for physical effort. They suffer from pulmonary hypertension and right heart failure. They often present with chronic limb oedemas. Other disorders, like hypertension, congestive left heart failure and diabetes, are also pervasive. OHS patients additionally tend to have a more impoverished socioeconomic background.

OHS patients' hospitalisations are more frequent and more prolonged than in non-OHS patients. They more often require intensive care and have higher global mortality than obese individuals without OHS. Overall, in-hospital mortality of patients with OHS is 15% in acute-on-chronic respiratory failure; survivors of hospitalisation had reported 3-year mortality of 19%.

The strong association of OHS with OSA is the reason why two-thirds of patients are diagnosed when referred to a sleep laboratory for snoring. One-third of patients tend to be diagnosed when hospitalised for acute-on-chronic respiratory failure triggered by any cause, for example, a respiratory infection.

OHS is a vastly underdiagnosed and misdiagnosed disease. It is commonly judged as COPD exacerbation when presented in an acute state. Reportedly 43% of 600 hundred patients were misdiagnosed with COPD. Delay in the diagnosis of OHS causes a more significant economic burden on the whole health care system.

Investigations:

Saturation of oxygen measured by pulse oximeter (SpO_2) may be a useful screening tool. Combination of $SpO_2 < 95\%$ and forced vital capacity (FVC) < 3,5 L in men, an $SpO_2 < 93\%$ and FVC < 2,3 L in women is highly suggestive of OHS. Similarly, nocturnal saturation decreasing under 80% is suspicious for OHS. The increased concentration of venous bicarbonate (HCO_3^- > 27 mmol/L) also indicates chronic hypoventilation.

Definitive confirmation of OHS requires either daytime **arterial blood gases** (ABGs) where daytime hypercapnia is present or nocturnal monitoring of carbon dioxide (**capnometry**, usually part of a sleep study). Other potential causes of hypoventilation should be excluded in every patient, notably COPD (no obstruction in pulmonary function tests), chest wall deformities or neurological causes.

Due to the close association of OHS with OSA, a **sleep study** is strongly recommended, ideally complete overnight PSG with capnometry, or at least polygraphy, in a patient in a stabilised state. The presence or absence of OSA determines the phenotype of OHS and may influence the strategy of ventilatory therapy.

Very few patients, about 5-10%, have no significant OSA; we could call their phenotype "pure hypoventilation". On the other hand, some OHS patients have very severe OSA with interapnoeic intervals so short that they do not allow compensatory hyperventilation. They do not necessarily have to have significantly impacted ventilatory mechanics, and they might profit from the simple abolition of OSA by CPAP. Most patients, however, are a combination of these two borderline phenotypes.

Treatment of OHS

The most casual approach to resolving OHS is **weight reduction**. Diet and lifestyle modifications are strongly recommended. If they are not sufficient, bariatric surgery is an option. Pulmonary physiotherapy is convenient for improving patients' breathing patterns.

The most immediate intervention that can be applied to relieve respiratory failure is **non-invasive ventilation** (NIV) or **positive airway pressure** (PAP) therapy. The NIV principles have been introduced in the chapter about OSA and are further explained in the

chapter about respiratory failure. **CPAP** is recommended in patients with a more pronounced OSA phenotype and should be tried in all patients with OSA unless severe hypercapnia is present. It allows the abolition of apnoeic episodes and recruits dystelectatic alveoli in the basal parts of the lungs. **BiPAP** therapy is used to relieve hypoventilation by deepening tidal volume. It is a more frequently used option than CPAP.

Nonetheless, the long-term effects of both CPAP and BiPAP are comparable in terms of blood gases, daytime sleepiness, quality of life, polysomnographic parameters, days of hospitalisation, cardiovascular events, and survival. Being the cheaper and more accessible option, CPAP is recommended to be tried after normalising blood gases and restoration of respiratory centre sensitivity. In case NIV does not achieve significant improvement of hypoxemia, oxygen therapy is added.

It is important to stress that **in chronic hypoventilation, the sensitivity of the respiratory centre to changes in $PaCO_2$ and pH is diminished**. Any decrease of pH in cerebrospinal fluid is buffered by bicarbonates retained in high concentration. The respiratory centre reacts more readily to hypoxaemia indirectly mediated by peripheral chemoreceptors. The oxygen therapy, mainly in a higher flow rate, removes the hypoxaemic stimulus for the respiratory centre, further promoting hypoventilation. Notably, in the case of acute-on-chronic respiratory failure in decompensation of OHS, when a patient complains of dyspnoea and oxygen saturation is severely reduced, it is intuitive to apply oxygen by an oxygen mask. This action, however, can be detrimental to ventilatory regulation and can proceed to hypercapnic coma. **Oxygen therapy as a solitary measure should be administered cautiously and only if NIV is not available/not tolerated by the patient, at a low flow rate, e.g., 1-2 L/min**, while monitoring blood gases closely. This approach is valid for all cases with supposed chronic hypoventilation.

NIV with or without oxygen therapy is applicable both in a stabilised patient at home and in a sudden worsening of the clinical state in the hospital. If NIV is unsuccessful, i.e., progression of hypercapnia or worsening of consciousness occurs, intubation might be unavoidable, or in case of home treatment, application of invasive ventilation by tracheostomy.

HYPOVENTILATION IN KYPHOSCOLIOSIS AND NEUROMUSCULAR DISORDERS

Kyphoscoliosis and neuromuscular disorders are examples of diseases leading to severe restriction of the chest. Still, the pulmonary tissue is intact unless vasoconstriction and remodelation of arterioles occur and pulmonary hypertension develops. The chest wall is either deformed, weakened or both. In neuromuscular patients, muscle weakness can extend to the oropharynx and cause obstructive sleep apnoea. Respiratory muscle weakness can also manifest as sudden deep hypoventilation and result in a temporary halt in breathing which constitutes nonobstructive central apnoea.

In kyphoscoliosis, neuromuscular disorders and similar diseases with a highly restrictive pattern, sleep study, ideally with capnometry, is recommended. The presence or absence of sleep apnoea influences ventilatory strategy. Monitoring nocturnal saturation can be more informative than daytime saturation. Also, nocturnal hypoventilation precedes the beginning of daytime hypercapnia. If capnometry is not available, the ABGs immediately after awakening in the morning can reflect nocturnal hypoventilation. Nocturnal hypoventilation can present with morning headaches and a sense of non-restorative sleep. If the patient mentions these complaints, the presence of nocturnal hypoventilation should be addressed.

Timing of the beginning of the treatment by non-invasive ventilation is crucial, as NIV, airway clearance therapies, and home saturation monitoring prolong the patients' survival. BiPAP is an option of choice if necessary, assisted by oxygen therapy.

HYPOVENTILATION IN OBSTRUCTIVE DISORDERS

COPD, diffuse bronchiectasis, and cystic fibrosis are the most frequent conditions with worsening of hypercapnia during sleep, especially REM sleep.

Notably, in COPD, as the most prevalent of these diseases, the problem of hypoventilation at sleep is very complicated. Even in the daytime, in COPD, there might be an ineffective ventilatory mechanic and respiratory muscle weakness. If a patient is obese, the same components as in OHS may overlap. **Obese COPD patient** with increased risk for OSA has been recently proposed as a defined phenotype. Hence, in COPD patients, a sleep study is recommended. If OSA and/or nocturnal hypoventilation are present, NIV is the treatment of choice, with settings adjusted explicitly for patients with a need for longer expirium and with the fragility of damaged pulmonary parenchyma in mind. Long-term NIV in COPD reduces the frequency of exacerbations and reduces mortality.

7 CHRONIC COR PULMONALE

Chronic cor pulmonale (cor pulmonale chronicum)

- **Pulmonary heart disease**, ***cor pulmonale*** (CP), can be defined as a pathological condition with a disorder of the right ventricular structure and function due to its acute, intermittent, or persistent congestion associated with **pre-capillary pulmonary hypertension**
- The development of chronic CP is due to lung, thoracic wall or ventilatory disorders with **hypoxaemia** as well as pulmonary vascular disease - chronic thromboembolism and primary involvement of pulmonary arteries - pulmonary arterial hypertension
- The main symptom is progressive **dyspnoea** and intolerance of physical exertion, the objective signs on the heart include **accentuation of the pulmonary component of the second heart sound**; distant features are **jugular vein distension, hepatosplenomegaly, ascites**, peripheral **oedema** up to **anasarca**
- Diagnostic signs of chronic CP can be found on the **electrocardiogram** and **chest X-ray**, assessment of right ventricular morphology and function, and **echocardiography** estimation of pulmonary pressure; the most accurate method for examining haemodynamic conditions in the pulmonary circulation is **pulmonary angiography**
- The focus of treatment is the **correction of hypoxaemia** with long-term oxygen therapy or non-invasive ventilation; pharmacotherapy of symptomatic right ventricular failure is based on the administration of **diuretics**. In the case of thromboembolism, long-term **anticoagulation** is necessary

DEFINITION AND EPIDEMIOLOGY

The term *cor pulmonale* was first used by White in a 1931 description. In 1963, the Panel of World Health Organization experts agreed on the pathological-anatomical definition of *cor pulmonale*, according to which right ventricular hypertrophy is a consequence of diseases affecting lung function or structure, *except* lung manifestations of left-sided heart disease and congenital heart defects. Subsequently, the term "hypertrophy" has been replaced by the term "alteration in the structure and function", which also includes all changes in morphology and function of the right ventricle, not only overt hypertrophy.

To develop these changes in the structure and functioning of the right ventricle, an increase in blood pressure in the arterial part of the pulmonary stream, i.e., **pulmonary hypertension** (PH), must be present. Therefore, in the simplest way, **cor pulmonale** (CP) can

be defined as a pathological condition with a disorder of right ventricular structure and function due to its acute, intermittent, or permanent overload due to precapillary PH. The term "precapillary" means that the pulmonary artery pressure is increased at normal (non-elevated) wedge pressure (in the pulmonary capillary) corresponding to the left atrial pressure. **Precapillary PH** results from diseases that affect the function or structure of the lung itself, the pulmonary vessels, or the diseases of the chest cage. Thus, it does not include left ventricular failure (whether due to myocardial disease or aortic and mitral valve failure) or congenital heart failure with a left-to-right shunt. Depending on the time course of the disease, we recognize **acute cor pulmonale**, which changes over several hours to days, and **chronic cor pulmonale**, with the development of changes over months to years.

The most common cause of a sudden increase in pulmonary pressure is pulmonary embolization (thrombotic and non-thrombotic) with occlusion of the pulmonary artery and its branches. Signs of hypertrophy of the right ventricle, unless previously caused by other causes, are not in the developed form in acute CP. This chapter deals mainly with chronic CP, which is the result of a longer-lasting and usually slowly increasing pressure overload of the right ventricle. However, dilatation and failure of the right ventricle may occur with any form of CP.

The most common causes of chronic CP are chronic respiratory diseases associated with PH, and first, **chronic obstructive pulmonary disease** (COPD) with the highest prevalence worldwide. Exact data on the incidence and prevalence of PH in respiratory diseases are unknown. It is estimated that within one year, CP develops in about 6% of COPD patients, and morphological signs of right ventricular hypertrophy are present at autopsy in up to 40% of COPD patients. There is even less data on the incidence of CP in other lung diseases.

ETIOPATHOGENESIS AND CLASSIFICATION

Pulmonary hypertension (PH) is defined as by **increase of mean pulmonary artery pressure above 25 mm of mercury (mmHg)** at rest**.**

The main causes of PH are**:**

1. Pulmonary parenchyma diseases or conditions with alveolar hypoventilation, the common sign of which is hypoxemia,

2. Pulmonary vascular diseases such as chronic thromboembolic disease or primary pulmonary artery disease - pulmonary arterial hypertension, and

3. Diseases of the myocardium or valvular apparatus of the left heart, a common feature of which is increased pressure in the left atrium.

The first and second groups of disease states are associated with **pre-capillary PH** (pressure increases at pulmonary arterioles, and left atrial pressure is not elevated). Myocardial and left ventricular valve diseases are associated with **post-capillary PH**, which is **not the cause of chronic cor pulmonale** – that is, isolated right ventricular failure – but leads to the development of biventricular heart failure. A comprehensive and simplified version of the clinical classification of PH in children and adults is presented in Table 7.1. This classification includes all categories of disorders with PH.

Table 7.1. Updated clinical classification of pulmonary hypertension (PH) (simplified)

Type of PH
1. Pulmonary arterial hypertension (PAH)
2. PH due to left heart disease
3. PH due to lung diseases and/or hypoxia
4. PH due to pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms

A detailed classification of lung diseases or conditions with hypoxemia (listed in category 3) that result in the development of chronic CP based on the hypoxic form of pre-capillary PH is shown in Tab. 7.2. COPD has a leading position in terms of frequency and relatively common causes of PH include diffuse parenchymal lung disorders, pneumoconiosis, kyphoscoliosis, sleep apnoea syndrome, obesity hypoventilation syndrome, and cystic fibrosis.

Table 7.2. Respiratory diseases and conditions with hypoxemia associated with pulmonary hypertension and the development of chronic cor pulmonale

Obstructive lung diseases
▪ Chronic obstructive pulmonary disease (COPD) ▪ Asthma with irreversible airway obstruction ▪ Cystic fibrosis ▪ Bronchiectasis ▪ Obstructive bronchiolitis
Restrictive lung diseases
▪ Neuromuscular disorders (amyotrophic lateral sclerosis, myopathy, diaphragm paralysis) ▪ Kyphoscoliosis ▪ Thoracoplasty ▪ Post-tuberculosis sequelae ▪ Sarcoidosis ▪ Pneumoconiosis ▪ Drug-induced lung disease ▪ Hypersensitivity pneumonitis ▪ Connective tissue diseases ▪ Interstitial lung diseases
Diseases associated with hypoventilation
▪ Central hypoventilation syndrome ▪ Obesity hypoventilation syndrome ▪ Sleep apnoea syndrome

Hypoxaemia is a powerful stimulus for pulmonary vasoconstriction. Hypoxaemia can be **continuous** (e.g., in COPD) or **intermittent** (in sleep apnoea). Another important mechanism associated with PH is **loss of pulmonary vascular bed**, often present in emphysema and fibrotic lung diseases. A key factor in the development of chronic CP is the long-lasting **load of the right ventricle (RV)**, resulting from the gradually increasing pulmonary vascular resistance due to PH. Long-term increased demands on the right ventricle result in structural changes, **hypertrophy,** and later **dilatation**, conditional on increasing the dimensions of its walls and cavities. Structural changes and overload are manifested by right ventricular dysfunction, which may be systolic or diastolic. **Right ventricular dysfunction** is defined by the presence of dysfunction or contractility, detectable by abnormal values of a variety of measurable indicators, which may or may not manifest clinically. One of the most used indicators of function is the right ventricular ejection fraction.

Right-ventricular failure is already a developed complex clinical syndrome, the main manifestations of which are:

1. Fluid retention with peripheral oedema, ascites to anasarca,
2. Decrease in systolic cardiac output with hypotension, fatigue, and intolerance of physical exertion; and
3. Supraventricular or ventricular dysrhythmias.

Right ventricular **muscle hypertrophy** is a compensation mechanism for increased pulmonary vascular resistance. End-diastolic pressure in the right ventricle does not initially increase and maintains both systolic ejection volume and ejection fraction. However, as **dilatation** increases, an increase in the end-diastolic filling is required to maintain the same systolic ejection volume, thereby reducing the **right ventricular ejection fraction**. Therefore, factors that may limit right ventricular filling in diastole (reduced compliance with advanced free wall hypertrophy, oppression in widespread emphysema) ultimately result in a decrease in **systolic output**. In the case of hemodynamically compensated CP, **right ventricular contractility**, assessed from end-systolic pressure to volume ratio, is normal. When the triggering factor occurs, for example, in the acute deterioration of the underlying respiratory disease, end-diastolic filling pressure rises to reach the maximum limits of end-diastolic filling as the last compensatory mechanism for sustaining systolic output while suddenly further increasing pulmonary vascular resistance. Increased end-diastolic pressure in the dilated right ventricle results in limited emptying of the right atrium and results in **systemic venous congestion with peripheral oedema**. However, swelling as a classic manifestation of the manifest failure of the right ventricle cannot be understood solely in a mechanistic way. Other mechanisms **include sodium and water retention** due to activation of the renin-angiotensin system, increased adiuretine secretion and impaired regulation of natriuretic peptides. The presence of **hypercapnia** (with its peripheral vasodilatory effect), if present in the picture of respiratory insufficiency, also has a noticeable effect.

The right and left heart compartments are functionally connected in series (sequentially) and separated by pulmonary circulation. Therefore, in the **stages of advanced heart failure**, reduced systolic output of the right ventricle leads to a decrease in diastolic filling and a decrease in both systolic and left ventricular output, particularly through reduced venous return from the pulmonary veins. There is a decrease in pressure in the aortic bulb and a reduction in the right coronary artery. **Right ventricular myocardial ischemia** is reflected in the further progression of its dysfunction. In addition, **tricuspid valve regurgitation** generally

deteriorates the efficiency of the dilated right ventricle. Adverse conditions for myocardial work in both ventricles are, in addition to systemic hypotension, potentiated by hypoxia and developing acidosis.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical features

Diagnosis of pulmonary hypertension is performed per exclusionem. In a personal history, we look for known chronic lung, airway, or respiratory control disorders. We search for performed surgical procedures on the chest or possible chest deformities. When a thromboembolic disease is suspected, we search for overcome deep venous thromboses, especially in the lower extremities, as well as congenital and acquired thrombophilia. Also noteworthy are data on systemic connective tissue disease, anorectic use, HIV infection or chronic hepatitis, which are possible causes of rare pulmonary arterial hypertension.

Symptomatology. Common symptoms of CP include:

• **Dyspnoea** – may be a manifestation of basic lung disease and may become more pronounced with the development of right ventricular failure

• **Reduced physical exercise tolerance** – sometimes described as fatigue or weakness

• **Impaired digestion** – right upper quadrant discomfort associated with congestive hepatopathy

• **Oliguria and nycturia** – due to decreased organ perfusion

• **Thoracic pain** (on exertion) – difficult to be distinguished from stenocardia in left ventricular myocardial ischemia.

• **Syncope** – rarely in decreased systolic cardiac output

• **Peripheral oedema** – may not be present in the lower limbs even in severe PH and are rare in normocapnia. Their occurrence is prognostically severe, especially with concomitant hypercapnia, and survival is very limited.

The physical examination allows us to recognize **heart symptoms and distant signs**.

Symptoms on the heart include an **accentuation of the pulmonary component of the second heart sound – P2** (in the second left intercostal space), which appears over a long-lasting PH. Symptoms of right ventricular hypertrophy may be **systolic pulsation** (parasternal

heave) to the left at the lower edge of the sternum and the epigastrium. An additional S3 (**proto-diastolic gallop**) caused by right ventricular failure or S4 heart sound (the **presystolic gallop**) caused by right ventricle hypertrophy can be present. Dilatation of the right ventricle (and valvular annuli) results in pulmonary and **tricuspid valve insufficiency**. The tricuspid regurgitation is evidenced by a **systolic regurgitation murmur** with a maximum above the lower edge of the sternum. Its intensity increases in inspiration (unlike the mitral valve murmurs), while the loudness of the murmur does not correspond to the severity of the valve disease (a slower regurgitation flow with significant regurgitation is manifested by a quiet murmur). **Graham-Steel's diastolic murmur** associated with pulmonary valve regurgitation can be heard best at the left sternal edge in the second intercostal space, spreading along its left edge down.

Distant signs of CP include **cyanosis** and **cachexia**. In emphysema, **orthopnoea** is a frequent finding associated with the negative effect of pulmonary hyperinflation on venous return and right atrial filling. Examination of the neck reveals a **raised jugular venous pressure** (filling). **Hepatojugular reflux** is manifested by an increase in jugular vein load during palpation of the liver area. **Hepatomegaly** can be objectified by palpation and hatch; congestive splenomegaly is less common. The picture of a generalised swelling state in the context of secondary hyperaldosteronism besides peripheral swelling of limbs includes **ascites**, **pleural effusion**, and eventually even **anasarca**.

Investigations

Diagnosis of CP is based on a detailed medical history, physical examination, use of basic auxiliary examination methods (electrocardiography, chest X-ray, echocardiography, laboratory examination, lung function testing) and specialized diagnostic procedures (special imaging methods, polygraphy, right heart catheterisation) differentiation of individual causes of CP.

Electrocardiography (ECG) is not a highly sensitive method but can be helpful in the diagnosis of CP by detecting right ventricular hypertrophy, enlargement of the right atrium or PH.

Right ventricular hypertrophy with increasing myocardial mass gradually leads to a predominance of the right ventricular depolarization vector. The first thoracic lead (V1) is located closest to the right-ventricular myocardium, and we observe an increase in the amplitude of the R wave. The electric axis in the limb leads is deviated to the right. Secondary

changes in the repolarization phase may occur in the right-side thoracic leads. The manifestations of right ventricular hypertrophy on ECG are summarized in Tab. 7.3. The dominant increase of R wave in V1 and right axis deviation are not specific only for the right ventricle hypertrophy but may also occur in other heart conditions.

Table 7.3. Diagnostic criteria for right ventricular hypertrophy on ECG*
(according to Harrigan and Jones, 2002)

Diagnostic criteria
▪ Right axis deviation of ≥ +110°
▪ Dominant R wave in lead V1 (> 7 mm tall or R/S ratio > 1)
▪ Dominant S wave in lead V5 or V6 (> 7 mm deep or R/S ratio < 1)
Supporting criteria
▪ ST segment depression / T wave inversion in the leads V_1 – V_4 (RV strain pattern)
▪ Deep S waves in lateral leads (V_5, V_6, I, aVL)
▪ Right bundle branch block (incomplete)

* provided that the duration of the QRS complex is less than 0.12 seconds

Right atrial enlargement (based on hypertrophy and dilation of the atrial myocardium) is manifested by the dominance of the right atrial depolarization vector directed forward and downward and depicts the initial phase of the P wave. The result is a high amplitude of the P wave (≥ 2.5 mm), the duration of which is usually not prolonged, and the image referred to as ***P pulmonale***, is best observed in inferior leads II, III and aVF. It is necessary to mention the possibility of **heart rhythm disorders** in the field of structural changes of atrial and ventricular myocardium and may be contributed by hypoxia, exacerbation of underlying lung disease and used pharmacotherapy. Supraventricular arrhythmias (atrial fibrillation and flutter, atrial extrasystoles, multifocal atrial tachycardia) are most reported; ventricular extrasystoles and tachycardia may also occur.

Chest X-ray (PA and lateral projection) has a special position among imaging methods due to its fundamental importance in the differential diagnosis of respiratory diseases. We are looking for signs of PH and CP and manifestations of the underlying disease that caused PH.

The diameter of *truncus intermedius* (of the right pulmonary artery) greater than 16 mm in the PA view, possibly in combination with the extension of the descending branch diameter of the left pulmonary artery in the left lateral projection above 18 mm, reliably identifies the presence of PH.

Other X-ray signs of CP and PH include:

• prominence of the right edge of the heart silhouette when enlarging the right ventricle

• prominence of the pulmonary arch to the left above the left atrium

• relatively oligemic peripheral areas of the lungs due to vasoconstriction, with simultaneous central pulmonary arteries enlargement

Chest X-ray also contributes to the differential diagnosis of symptoms and demonstrates evidence of lung and cardiac disorders that might be the cause of PH. Signs of pulmonary infarction, wedge-shaped peripheral consolidations, belong to the image of pulmonary embolism. Rarely we can see the oligemic region beyond the location of the lining of the lung artery branch - the *Westermark sign*. X-ray signs of emphysema, bronchiectasis, diffuse parenchymal lung disorders, or kyphoscoliosis point to the cause of PH. Cardiomegaly with a dominant extension of the left ventricular shadow or its characteristic configuration (aortic, mitral) points to diseases of the left ventricle, atrium, or valvular apparatus with the development of post-capillary PH, which is not CP despite the presence of increased pulmonary pressure.

Transthoracic echocardiography allows non-invasive estimation of pulmonary pressure by measuring the maximum velocity of the tricuspid regurgitation jet in continuous Doppler mode. It is the only non-invasive test that can measure pulmonary artery pressure.

The standard two-dimensional imaging allows the **evaluation of the morphology** and dimensions (wall thickness and cavity diameter) of the **right ventricle, right atrium, and left ventricle**, along with the configuration of the interchamber septum. Assessment of **right ventricular systolic function** is one of the major domains of echocardiographic examination of right-sided heart sections but is much more complex than in the left ventricle. The differential diagnostic benefit of the examination consists in distinguishing left ventricular dysfunction or mitral valve disorder as the cause of pulmonary venous hypertension. The limitations of the

examination are suboptimal echogenicity in patients with severe pulmonary hyperinflation or extreme obesity.

Other imaging methods. A less used method in specialized centres is **magnetic resonance imaging,** which provides the most accurate representation of right ventricular and atrial morphology, as well as assessment of right ventricular systolic function. It is also useful in severe emphysema. **Radionuclide ventriculography** allows non-invasive determination of the right ventricular ejection fraction (using radioactive material Technetium-99m) and thus indirectly assessing its systolic function. **Computer tomography** examination is particularly beneficial in the differential diagnosis of lung and pulmonary vascular diseases as a cause of chronic CP. In high-resolution (HRCT) mode, it diagnoses disorders of lung interstitium, and using intravenous contrast verifies embolic obstruction of pulmonary artery branches. In addition, the diameter of truncus pulmonalis also correlates with pulmonary pressure.

Blood tests. Basic laboratory examinations in the diagnosis of causes of chronic CP include examination of **arterial blood gases** and **acid-base balance**. Hypoxemic respiratory insufficiency is a direct pathogenetic link between chronic respiratory diseases and CP. However, hypoxemia is also a potent vasoconstrictor stimulus that worsens PH. In the **blood count**, we look for reactive polyglobulia, high haematocrit and increased haemoglobin concentration due to chronic hypoxemia; the basic parameters of haemostasis are platelet count. If pulmonary embolism is suspected, it is necessary to investigate the baseline **coagulation markers**, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer.

Examination of the **brain natriuretic peptide** (BNP) serum concentration may be beneficial for the detection of PH in patients with chronic lung disease. It is a neurohormone, despite its name, synthesized mainly in the ventricles of the heart and released into the circulation in response to increased ventricular wall tension as the end-diastolic blood pressure rises. Its concentration may be affected by age and gender. A marked increase in circulating values, usually above 400 pg/mL, has been reported in patients with congestive left ventricular failure. However, in the range of 100 to 400 pg/mL PH with CP, acute pulmonary embolization or left ventricular dysfunction without volume overload should be considered. In the absence of PH, serum concentrations are generally well below 100 pg/mL. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is an inactive protein that is cleaved from the molecule BNP. It is chemically more stable than biologically active BNP, which is degraded in the circulation, so its use in biochemical assays is preferable.

Lung function testing, sleep study, exercise capacity testing.

Lung function testing, including spirometry, body plethysmography and measurement of *transfer factor* (diffusing capacity for carbon monoxide), is a mainstay for the diagnosis of lung disorders with obstructive and restrictive ventilatory impairment (Table 7.2.). The causal link between pulmonary involvement and CP development is indicated by the current finding of hypoxemia in arterial blood gas examination. Repeated intermittent hypoxemic episodes may also lead to CP manifestations in conditions associated with hypoventilation (Table 7.2.), where it is preferable to use **screening with transcutaneous oximetry** (nocturnal), preferably supplemented by **capnometry**. The gold standard for confirming and accurately determining the type and severity of a sleep disorder is a **polysomnographic examination**. A severe decrease in **transfer factor** in subjects without signs of significant ventilation disorder is a characteristic finding in pulmonary arterial hypertension. In patients with obstructive ventilation disorder and COPD, the relationship between the severity of the airflow obstruction and the rising pulmonary artery pressure is evident, but the progression of PH is gradual and tends to be mild to moderate, even in patients with the most severe degree of obstruction. A rarer form of PH in COPD patients, characterized as „*out-of-proportion"*, is severe grade PH at a less severe degree of airway obstruction, together with a marked decrease in lung diffuse capacity, more severe hypoxemia, hypocapnia and reduced cardiac output. In this type of PH, another cause of PH should be considered, such as chronic thromboembolic pulmonary hypertension (CTEPH). The exercise capacity assessment has a predictive value for several forms of PH and is also an important indicator in assessing the effect of pharmacological treatment and non-pharmacological interventions such as rehabilitation. In practice, **spiroergometry** and a **six-minute walking test**, which is simple and proven to be predictive of prognosis, are most used to assess the exercise capacity of patients with PH.

Right heart catheterisation is the gold standard in determining the exact values of blood pressure (systolic, diastolic, and mean) in lung circulation. It also allows the measurement of transpulmonary gradient and cardiac output as well as the calculation of pulmonary vascular resistance. It is an invasive procedure and should be generally reserved for the diagnosis of pulmonary artery hypertension (mostly idiopathic), in which specific vasodilatory therapy is considered and, at that time, additional vasoreactivity testing for vasodilatory drugs (nitric oxide inhalation, intravenous adenosine or epoprostenol) is required. Indications for right-sided cardiac catheterization are summarized in Tab. 7.4.

Table 7.4. Indications for right heart catheterization (according to Girgis and Mathai, 2007)

- severe symptomatic PAH with consideration of specific vasodilator therapy
- the need to assess for the left heart disease
- to determine the need for long-term oxygen therapy when PaO2 ≥ 8 mm kPa (60 mmHg)
- pre-operative (major surgery, lung volume reduction, lung transplant)
- severe PH „out-of-proportion" in relatively mild lung disease

PAH – pulmonary artery hypertension, PH – pulmonary hypertension, PaO_2 – partial pressure of oxygen arterial blood

TREATMENT

Treatment of underlying disease and lung complications. Destabilization of the underlying disease (e.g., acute worsening of hypoxemic respiratory insufficiency in COPD exacerbation) is a potent precipitating factor for a sudden increase in pulmonary vascular resistance. The dilated right ventricle, despite further compensatory increases in end-diastolic pressure, is unable to sustain systolic output, emptying of the right atrium is reduced, and systemic venous congestion develops with a clinical picture of right ventricular decompensation. Therefore, one of the first treatment steps for patients with CP should be to **optimize the treatment of the present chronic lung disease** and to **treat the exacerbations** vigorously. Prevention in the form of a pneumococcal and influenza vaccine and early antibiotic **treatment of respiratory infections** are recommended as the possible development of pneumonia in the field of chronic lung disease with developed CP increases the risk of mortality.

Oxygen therapy and non-invasive ventilation.

Home-based long-term oxygen therapy used for at least 15 hours per day has been shown to reduce mortality. The mechanism is a reduction of pulmonary artery pressures by reversing hypoxia-driven vasoconstriction.

Non-invasive ventilation, applied by a mask (nasal, oronasal or full-face mask) of positive air pressure to the airways, represents a therapeutic modality for PH because of chronic alveolar hypoventilation (chest wall diseases, neuromuscular diseases, obesity hypoventilation syndrome).

Pharmacotherapy.

Specific vasodilator therapy reduces vascular resistance of the pulmonary stream in rare severe forms of *pulmonary arterial hypertension*. It is characterized by an antiproliferative and anti-remodelling effect in the arterial part of the pulmonary circulation through intervention in the mediator systems responsible for vasoconstriction and remodelling of the pulmonary arteries. Drugs of the **prostaglandins (*epoprostenol*)**, **endothelin receptor blockers (*bosentan, sitaxsentan*)** and **phosphodiesterase-5 inhibitors (*sildenafil*)** are used. However, vasodilatory drugs are not suitable for the treatment of much more common other forms of PH. In diseases with alveolar hypoxia, vasodilation in the pulmonary stream causes an increase in the ventilation-perfusion ratio, leading to worsening of hypoxemia. Therefore, specific vasodilator therapy used in the treatment of pulmonary arterial hypertension is not indicated in CP due to pulmonary disease. **Anticoagulant therapy** is strongly recommended for the treatment of pulmonary arterial hypertension as well as PH associated with chronic thromboembolism (prevention of pulmonary embolism).

Irrespective of the type of PH that led to the development of chronic CP, **diuretics** are the focus of treatment for symptomatic right-ventricular failure. Highly effective loop diuretics such as ***furosemide*** favourably affect the right ventricular overload and help to reduce peripheral oedema. Hypokalaemia can be prevented by concomitant administration of ***spironolactone***, which has the additional benefit of inhibiting the renin-angiotensin-aldosterone system. In some cases (drug-induced gynecomastia), it may be replaced by the administration of ***eplerenone***. Diuretics should be administered with caution while monitoring electrolytes and fluid balance, as unwanted intravascular volume depletion may also result in a decrease in systolic ejection volume of the ventricles. Finally, bicarbonate accumulation due to diuretic therapy may lead to worsening of hypercapnia. Oedema in uncorrected hypercapnia is typically refractory to diuretic therapy unless carbon dioxide is effectively exhaled. The use of ***digoxin*** is limited to situations where symptomatic left ventricular heart failure and atrial fibrillation are present.

At the same time, **correction of hypoxemia** by application of **oxygen** is necessary. Caution should be exercised when administering diuretics concomitantly, especially with hypokalaemia induced. Blood gases and pH should be monitored as hypercapnia with respiratory acidosis may further aggravate hypokalaemia. In indicated cases, **non-invasive ventilation** should be initiated. Right ventricular dysfunction avoids the administration of beta-blockers and verapamil-type calcium blockers due to their negative inotropic effect. Supraventricular arrhythmias are poorly tolerated in CP due to the lack of effective atrial

contraction in hypertrophic right ventricle filling. Therefore the recovery of sinus rhythm alone sometimes leads to a decline in the manifestation of manifest heart failure. Myocardial contractility can also be affected by **positive inotropic agents**, ***dobutamine*** and ***milrinone***. They should be administered in workplaces with intensive monitoring. The effect of both drugs is not specific to the right ventricle; on the contrary, they have a similar effect on the left ventricular myocardium (increase in cardiac output, decrease in pulmonary vascular resistance).

Interventions to reduce haematocrit. In chronic hypoxia, compensatory polyglobulia develops, manifested by increased haematocrit and increased blood viscosity. The risk of this condition is the clinical manifestation of **hyperviscosity syndrome**. It is a damage of target organs by ischemia due to unfavourable rheological properties of blood in microcirculation in a patient with polyglobulia. In pulmonary microcirculation, moreover, hyperviscosity is associated with local nitric oxide deficiency and causes an increase in hypoxic pulmonary vasoconstriction. **Therapeutic phlebotomy** (bloodletting, venesection) followed by intravenous volume replacement is indicated in patients with severely elevated haematocrit (over 55%) not responding to oxygen administration in long-term oxygen therapy. Improvement of symptoms and exercise tolerance is temporary, and the procedure should be repeated.

PROGNOSIS

Right-ventricular failure manifestation with peripheral oedema development is a classic indicator of adverse prognosis in patients with chronic respiratory disease, with a short survival since the onset of oedema. The only treatment modality that has been shown to increase the survival of these patients is long-term continuous oxygen therapy. This is probably due to the stabilization of pulmonary pressure, with a consequent reduction in the occurrence of episodes of right-ventricular decompensation, as well as an improvement in oxygen supply to vital organs. In terminal stages of chronic respiratory diseases such as COPD, idiopathic pulmonary fibrosis, or post-TBC sequelae, the level of pulmonary pressure becomes the strongest predictor of these patients' adverse short-term prognosis, independent of pulmonary function.

8 TUBERCULOSIS

Tuberculosis

- Tuberculosis (TB) is an infection caused by mycobacteria from the ***Mycobacterium tuberculosis complex***; and may affect any organ but most commonly affects the **respiratory system**
- Infection induces typical (specific) **inflammatory changes** in the tissues, characterized by the formation of **caseating granulomas** and the formation of pulmonary cavities
- Diagnosis is based on an epidemiological history, the presence of **general** and **respiratory symptoms** (weight loss, cough with sputum production and haemoptysis), **imaging** and **microbiological evidence** of mycobacteria, **histological examination** of tissues and **immunological tests** (tuberculin skin test and IGRA tests)
- Treatment is based on the **long-term application of combined antituberculotic chemotherapy** according to standard regimens, with adjustment in specific situations (drug resistance, HIV co-infection), and in some cases, surgical treatment (lung resections)
- **Vaccination with a live attenuated strain of BCG** has been a major tool in the past century to reduce the incidence of the disease, protecting against severe haematogenous disseminated forms of TB in children but not against adult TB

DEFINITION AND EPIDEMIOLOGY

Tuberculosis (TB) is a general infectious disease caused by pathogenic mycobacteria of the ***Mycobacterium tuberculosis complex*** group, including *M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti* and *M. pinnipedii*.

At present, in our conditions, there is practically only a disease caused by *M. tuberculosis* (Koch's Bacillus – see historical note) itself. Diseases caused by others, so-called nontuberculous (atypical) mycobacteria (*Mycobacterium avium complex, M. xenopi, M. kansasii, M. fortuitum, M. chelonei* and others), are called nontuberculous mycobacteria (NTM) infections (or mycobacterioses). Bacteria from this group, in contrast to tuberculosis, can also be present in the environment (water, soil, etc.), it is an opportunistic pathogen for humans, and the incidence of mycobacteriosis is higher in people with immunosuppression.

The most common **source of TB** for humans is a **person who is ill with a form of TB that excretes living bacteria in the environment**. This is mostly a sick individual with

pulmonary tuberculosis, and the bacteria are found in pulmonary secretions - in the **sputum**. In extrapulmonary forms of tuberculosis, excretions from diseased organs, glands, or skin ulcers can be a source of infection. In renal tuberculosis, the bacteria are found in the urine. Diseased animals are a rarer source of mycobacterial infection. Such infections caused by M. bovis after the elimination of sick cattle in the 1970s are currently rare.

The transmission of the disease occurs:

1. By **inhalation**, namely a) the so-called dry way – by inhalation of infected dust, or b) wet way - by inhalation of infected droplets of pulmonary or nasal secretion, etc. Inhalation of small droplets up to 5 millimicrons, which reach the alveoli, is serious. In a speech, the dispersion of such droplets is up to 0.5-1 meter, in coughing and sneezing up to 3 meters and beyond.

2. By **inoculation** – infection by direct contact with infectious material in case of damaged skin integrity occurs rarely in healthcare professionals, surgeons, pathologists, etc.

3. **Alimentary route** – foodborne transmission occurred in widespread tuberculosis of bovine animals. The source of the infection was unpasteurized and mainly uncooked milk and milk products.

The gateway to infection in humans is the most common respiratory system, which is confirmed by the predominance of pulmonary forms of tuberculosis. The less common entrance gate of the infection may be the digestive tract. The infection can also be caused by swallowing the infected sputum of the patient with the pulmonary form, but also by the bloodstream. The skin is the gateway to direct contact with the infection through its injured areas. From a diseased site, for example, in the lungs, the infection can be transmitted through the bloodstream to any organ that has a blood supply. A very rare form of infection transmission is the transmission of bacteria to the foetus in severe forms of tuberculosis in the mother.

Every second, one person in the world becomes infected with tuberculosis. The WHO estimates that 2 billion people have latent tuberculosis infection, 9 million people develop the active disease (1 million children), and 1.3 million die each year from TB. People with co-existing HIV infection account for about 1.2 million cases. The risk of infection differs between parts of the world. The incidence rate of TB is highest in Asia and sub-Saharan Africa (> 100 per 100 000). In high-income countries in Europe and North America, there are specific high-

risk groups, including people with HIV infection and AIDS, drug users, prison inmates, immigrants and persons infected with multidrug-resistant strains of tuberculosis.

In Europe, there is a big difference between Western, Central and Eastern Europe. According to the WHO, all countries of the former Soviet Union also belong to the European region. In Europe, up to 85% of bacteriologically confirmed tuberculosis is in the countries of Central and Eastern Europe. Most Western European countries have an incidence of less than 20 per 100,000 inhabitants, except for Spain and Portugal. Among the countries with a low incidence of tuberculosis, only Slovakia, the Czech Republic, and Slovenia are among the former countries of the Eastern bloc. On the contrary, from Eastern Europe, Romania and the Russian Federation show high numbers (incidence > 70 per 100,000). The Slovak Republic is one of the countries with a low incidence of TB, with a prevalence of 3.93 cases per 100,000 in 2019.

HISTORICAL NOTE

In history, awareness of the infectivity of tuberculosis has developed only gradually.

Galenos (129-199 AD) defines phthisis as pulmonary ulceration and is convinced of its infectivity. Remarkable is Galen's book on marasmus, which he calls the extinction of the living caused by ***phthisis and consumption***. Tuberculosis was also named the white death or white plague.

Robert Koch (1843 - 1910) became one of the greatest researchers of mankind in his work on the nature of infectious diseases. At a meeting of the Berlin Physiological Society on March 24, 1882, in a famous speech "Über Tuberkulose", he reported on his discovery of the tuberculosis bacillus, proving the bacterial nature of this infectious disease. In the work Die Aethiologie der Tuberkulose published in the Berliner Klinische Wochenschrift on April 10, 1882, Koch expressed the so-called **Koch's postulates**, which became the basis of bacteriological research:

1. The microorganism must be found in abundance in all organisms suffering from the disease but should not be found in healthy organisms.
2. The microorganism must be isolated from a diseased organism and grown in pure culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

PATHOGENESIS

Tuberculosis infection represents a complex interaction between the ***mycobacterium tuberculosis*** (the infectious agent) and the patient´s specific immune response. A characteristic course of infection starts with the inhalation of respiratory droplets containing bacteria. The bacteria then invade **alveolar macrophages**. If macrophages have fully functional effector mechanisms, mycobacteria are killed intracellularly. However, mycobacteria produce substances (ammonium sulphate, sulfatides, mycobacterial wall lipoglycans) that prevent their phagocytosis. A cell-mediated immune response tries to control the infection by creating a **granuloma** (tuberculoma) consisting of T cells and macrophages around infected cells. Epithelioid cells and TB-specific Langhans giant cells also form a granuloma. The formation of granulation tissue with epithelioid giant cells without central necrosis occurs in several diseases. They are, e.g., sarcoidosis, lues, viral lymphadenitis, tularemia, brucellosis, leprosy, beryllium, mycoses, and foreign body reactions. However, it is typical for tuberculosis that necrotic changes, also called **caseous necrosis**, occur in the centre of the granulation tissue in the tuberculosis nodule. By coughing up the caseous mass through the draining bronchus, a pulmonary cavern (cavity) is formed. However, the infection is not limited to the site of entry into the body. If the necrotic lesion is released into the bronchial system, bronchogenic dissemination occurs. Mycobacteria can also be released from damaged and decayed macrophages into the lymphatic vessels (lymphogenic dissemination) or into the blood vessels (haematogenous dissemination). Calcium phosphate, calcium oxalate, calcium carbonate and calcium sulphate salts often begin to deposit in the necrotic granuloma. Calcification takes place either centrally or on the periphery of the lesion and usually occurs more than six months after infection.

Immunopathogenic aspects of TB infection. After infection, mycobacteria significantly slow down their metabolism and adapt to the conditions in the phagosomes of the monocyte-macrophage system. The **antibody immune response is unlikely to play a protective role** in defence against *M. tuberculosis*. Infection can induce protective immunity but also an immunopathological reaction of delayed-type hypersensitivity (type IV hypersensitivity reaction, according to Coombs and Gell). In the lung, adhering *M. tuberculosis* is eliminated by alveolar macrophages. Compared to other species of non-tuberculous mycobacteria, m. tuberculosis has the ability not to release phosphorylated antigens into its environment. These phosphorylated antigens are a condition for rapid recognition by a specialized subset of human T-lymphocytes, which are a rapid source of **interferon gamma**

(IFN-γ) and are also capable of direct lysis of infected macrophages. **Cooperation between macrophages and specific T-cell immunity** is essential for the effective intracellular killing of mycobacteria in macrophages. An important part of this collaboration **is dendritic cells**, which are in the interstitium of the lungs, where they capture mycobacteria. These accessory cells, also called **antigen-presenting cells** containing *M. tuberculosis* antigens, are transferred to the regional lymph node. In the lymph nodes, these antigens are presented by T-lymphocytes. Thus, naive Th0 cells are polarized to **Th1 CD4 effector lymphocytes**. They can produce enough **IFN-γ** to activate alveolar macrophages. Alveolar macrophages, after stimulation, subsequently use a wide range of cytokines and **TNF-α** to kill mycobacteria.

The course of tuberculosis in the body. The most common gateway for tuberculosis into the body is the respiratory tract. By inhaling infected droplets 1-2 microns or less in size, the infection enters the alveoli. Larger droplets are excreted from the upper respiratory tract and bronchi.

If *M. tuberculosis* enters the lungs, several situations can arise:

a. The infection does not progress to clinically manifest disease; no foci are formed in the body. The tuberculin skin test in a tuberculin-negative individual remains negative; in a vaccinated individual, it has post-vaccination immunity values.

b. Microorganisms multiply, a specific inflammatory locus develops, clinically manifest **primary tuberculosis**

c. Microorganisms remain in a latent stage due to various factors; either a tuberculin skin test is converted, or a hyperergic reaction occurs, and the infection is not clinically manifest. A **latent stage** of the disease develops (latent TB).

d. Activation of microorganisms in the latent stage leads to clinical manifestation, **post-primary organ forms of tuberculosis** develop

DIAGNOSIS

Clinical features

Pulmonary tuberculosis – affects the pulmonary parenchyma. If there is both pulmonary and extrapulmonary involvement, it is classified as pulmonary tuberculosis. We do not classify tuberculous pleuritis and TB of the intrathoracic nodes among the lung forms unless the pulmonary parenchyma is also affected at the same time.

Extrapulmonary tuberculosis – can affect any organ of the human body, such as the pleura, lymph nodes, abdominal organs and peritoneum, the genitourinary tract (kidneys, adrenal glands, ovaries), the central nervous system and meninges, the sensory organs, bones and joints, and the skin.

Primary tuberculosis is characterized by a set of morphological changes in the affected organ after the first contact with mycobacterial infection. It most often occurs after inhalation of mycobacteria in the lung parenchyma, where a typical reaction occurs, the so-called **primary complex.** It appears on chest X-ray as a peripheral area of consolidation (**Ghon focus**) with hilar adenopathy. In most cases, spontaneous healing occurs due to the development of cellular immunity. The primary complex heals by **fibrotic transformation** and **calcification** of the lesion in the lungs, resorption of lymphangoitis and calcification of the affected lymph nodes. Primary pulmonary tuberculosis is characteristic of childhood and most often occurs as a clinically absent, asymptomatic form, which manifests itself in an unvaccinated individual only by **conversion of the tuberculin skin test** (after 4-6 weeks). By healing primary TB, the **individual acquires specific immunity to TB infection**. Rarely, in the case of immunodeficiency, there is a clinically manifest haematogenous generalization of primary TB (miliary TB, TB meningitis) or direct development into post-primary forms – lymphatic, haematogenous or bronchogenic dissemination. Due to compulsory **BCG vaccination (Bacillus Calmette-Guerin vaccine)** (1953-2012), primary tuberculosis is practically non-existent in our country (Slovakia) at present. In the vaccinated population, the primary complex forms in the regional lymph nodes (axillar) at the site of vaccine injection. Subsequently, like overcoming primary TB, the development of lifelong specific immunity is induced.

In **miliary tuberculosis** (milium = millet), mycobacteria can spread throughout the body through the bloodstream from a pre-existing tuberculosis lesion – haematogenous dissemination. When mycobacteria enter the bloodstream of the superior vena cava (from the

ductus thoracicus, from the perforated classified cervical node), the mycobacteria enter the lungs primarily through the pulmonary artery and form miliary pulmonary TB. If mycobacteria enter the systemic circulation (pulmonary vein), the infection will affect other organs. Miliary deposits are found in the liver, kidneys, spleen, bone marrow, heart, chorioid, serous membranes (peritoneum), meninges, endocrine glands, etc.

Post-primary tuberculosis is usually an organ-limited process in people who have already undergone primary infection. It is more often in adults. Repeated infiltration of tuberculosis bacteria into a post-infectious tuberculin-positive organism is called **exogenous reinfection**. In many cases, reinfection can result from so-called **endogenous reinfection** (**reactivation**) from foci with persistent *M. tuberculosis* mycobacteria. Factors predisposing to reactivation and the development of manifest disease are weakening of the body's immune status, for example, malnutrition, alcoholism, drug abuse, diabetes, and treatment with corticosteroids or immunosuppressants.

Respiratory tuberculosis is one of the most common manifestations. It includes airway involvement and lung parenchyma often associated with infection of the intrathoracic lymph nodes and pleura. The rate of mycobacterial proliferation is slower compared to other respiratory pathogens, leading to a characteristically chronic course of post-primary tuberculosis. **The onset of the disease is usually slow and obscure**. The worsening of patients' symptoms and clinical condition is gradual and may take weeks, with a subtle intensity of symptoms not necessarily recognized by patients or attributed to other circumstances (e.g., chronic smoker´s cough). Approximately one-third of patients may be asymptomatic at the time of the examination, and pulmonary tuberculosis is diagnosed accidentally on a chest X-ray during a routine check-up. The **general symptoms** include weakness and increased **fatigue**, **loss of appetite** and **weight loss** (therefore, TB was named as ***consumption***), **increased body temperature** – low-grade fever, and **night sweats** are typical. ***Febris inversa*** may be present when body temperature is higher in the morning than in the evening. The characteristic appearance of the face of people with TB – ***facies hectica*** (or ***amabilis***) is also described, as they were often young people with weight loss, pale skin colour and relatively prominent cheekbones, shiny eyes and noticeably lush hair and eyebrows, a special beauty in their expression (***beauté phthisique***). The most common organ symptoms of pulmonary tuberculosis (**respiratory symptoms**) are cough, expectoration, haemoptysis, pleural chest pain and, in extensive forms, dyspnoea. The intensity of the **cough** is variable. At the onset of the disease, it is unproductive, caused by the pressure of enlarged lymph nodes on the bronchi. Later,

a productive cough appears, associated with **sputum expectoration**. The sputum is usually mucous or purulent and usually contains mycobacteria tuberculosis, which is an infectious material associated with the risk of spreading the disease (it is called open tuberculosis). **Haemoptysis** can be a serious, life-threatening symptom of an active tuberculosis process with damage to the vascular wall by progressive necrosis and breakdown of the lung parenchyma. The blood from the lungs is bright red and foamy. **Pleural chest pain** occurs in fibrinous pleuritis over tuberculosis infiltrate or tuberculous cavity. Sudden severe chest pain, associated with new-onset dyspnoea, is a symptom of pneumothorax. **Dyspnoea** is associated with extensive lung parenchymal involvement, which can also lead to respiratory insufficiency. Rarely cyanosis occurs, with a chronic course also the club fingers and associated with the manifestations of cor pulmonale chronicum.

During the **physical examination**, we notice the overall appearance of the patient during the inspection. In the case of developed forms, there is a noticeable weight loss up to **marasmus**, which is also reflected in another name for TB – ***consumption***. We objectify increased body temperature, dyspnoea, tachypnoea, cyanosis, and clubbing fingers. Examination of the lungs is often normal but sometimes identifies crepitations or bronchial breathing. In tuberculous pleuritis, we can detect weakened breathing and dull percussion. By palpation, we look for enlarged lymph nodes in the neck, axillae, and inguinal regions.

The most common forms of pulmonary tuberculosis

- **Infiltrative tuberculosis of the lungs** – pulmonary infiltrates with exudation and a tendency to rapid caseous necrosis. The most common localization is the subclavian area but can affect any part of the lungs
- **Tuberculoma** – another form of infiltrate. It is a solid, round, bounded formation on a chest X-ray of the lungs resembling a tumour.
- **Cavernous tuberculosis** – a very infectious type. It develops through the breakdown of pulmonary infiltrate by caseous necrosis with subsequent expectoration of necrotic masses via draining bronchus
- **Nodular pulmonary tuberculosis** – the occurrence of nodules in the lung parenchyma, often with a poor clinical picture or asymptomatic
- **Tuberculosis pneumonia** ('Acute Pneumonic Phthisis') – an acute form with a rapid onset of severe symptoms of fever, shortness of breath and productive cough. The

sputum is purulent with many mycobacteria. Extensive pneumonic infiltration of the entire lobe of the lungs is typical.

- **Miliary tuberculosis** – this is a generalised form with a haematogenous spread of mycobacteria. Small nodules up to 1 mm in diameter (visible on a chest X-ray) and bilateral in the pulmonary wings are typical. The result of the tuberculin test is often negative (lack of immune response). May lead to the severe condition – respiratory failure, ARDS or sepsis (Landouzy's sepsis)

Extrapulmonary tuberculosis can move any organ or tissue. It occurs less frequently than pulmonary forms of tuberculosis (20% of all cases of TB). Most forms of extrapulmonary tuberculosis are caused by the haematogenous spread of mycobacteria from the original infectious site in the lungs.

- **Tuberculous pleuritis –** is one of the most common extrapulmonary manifestations of adult tuberculosis. Pleural involvement is usually unilateral, but in haematogenous dissemination, it can also be bilateral. In addition to non-specific general symptoms (low-grade fever, night sweats, weight loss), patients have a set of symptoms associated with the accumulation of fluid in the pleural cavity – pleural syndrome. To clarify its aetiology, **pleural puncture** with a biochemical, cytological and microbiological examination of the obtained fluid is required. Biochemically, it is exudate and a marker supporting the suspected TB aetiology of pleuritis is the increased activity of the enzyme ***adenosine deaminase*** (ADA) type 2 in effusion. ADA is an enzyme produced from lymphocytes and involved in purine metabolism. The test is simple, cheap, rapid, minimally invasive, and can be performed in most laboratories. High ADA levels can sometimes be observed in pleural fluid from patients with empyema, malignancy, or rheumatoid pleurisy. Cytologically, lymphocytes dominate. *M. tuberculosis* is confirmed by culture in only about a third of cases, so it is necessary to use other, highly sensitive methods of molecular biology (Polymerase chain reaction – PCR). If the aetiology of the effusion cannot be clarified, we proceed to pleural biopsy and histological examination.
- **Tuberculous lymphadenitis –** is another common manifestation of extrapulmonary tuberculosis. In most cases, these are the cervical nodes, which are painlessly swollen, there are frequent central fluctuations, and a fistula may be present on the outside of the skin.

- **Bone and joint tuberculosis** – is still a relatively common localization of extrapulmonary TB. The most common is spinal cord injury (spondylitis tuberculosa, Pott disease), where the process affects the body of the vertebra and spreads to an adjacent vertebra. Destruction leads to gibbus deformity, neurological manifestations (paraplegia) and often also to the development of cold abscesses (paravertebral and prevertebral, inguinal).
- **Central nervous system tuberculosis** – is a serious, life-threatening condition and includes meningitis (basilar), tuberculoma, and spinal arachnoiditis. Basilar meningitis occurs within a miliary TB and is dangerous due to the development of intracranial hypertension. Examination of the cerebrospinal fluid obtained by lumbar puncture is necessary. Brain tuberculoma is rare, behaves as an expansive brain process, and symptoms depend on the location of the disorder.
- **Urogenital tuberculosis** – first affects the kidneys and spreads to the ureter and bladder. In men, prostate involvement and epididymitis may occur. TB salpingitis is a possible cause of infertility in women.
- **Gastrointestinal tuberculosis** – infection of intestines, mesenteric lymph nodes (lymphadenitis) or peritoneum. It is manifested by abdominal pain, ascites, and catheterization.
- **Cutaneous tuberculosis** – may take the form of ulceration or nodular inflammation. Primary skin infection from an exogenous source or endogenous infection is possible.
- **Tuberculous otitis and ocular TB** – are most often caused by the haematogenous spread of infection. Tuberculous otitis occurs as a destructive inflammation in the middle and inner ear. Ocular TB can affect the external (keratoconjunctivitis) or internal eye structures, uvea (granulomatous uveitis), chorioid and retina.

Investigations

Diagnosis of tuberculosis is based on:

1. Detailed medical history, evaluation of the epidemiological situation, clinical examination
2. Imaging – Chest X-ray (PA projection), CT examination, etc.
3. Microbiological examinations
4. Endoscopic examination (bronchoscopy)
5. Histological examination

6. Tuberculin sensitivity
7. Detection of latent TB infection

Medical history is the first and very important step. We focus first on the personal history of the patient and overcome diseases. A very important issue is the health condition in the family, in the patient's immediate vicinity, and data on the people with whom the patient comes into contact. Accidental contact with a suspect over time in relation to the disease is an important indication.

Chest X-ray is another important criterion for making a diagnosis. The basis is a postero-anterior (PA view) or an X-ray of another organ. According to finding, the physician prescribes other types of imaging examinations such as CT examination (chest, abdomen, brain), magnetic resonance imaging (suitable for brain or joint involvement) or ultrasonography. The **primary TB complex** (Ghon focus) is most often found in the middle and upper lung fields and appears as a peripheral area of consolidation with hilar adenopathy. The size is a few millimetres but can also be larger. The X-ray image of **miliary tuberculosis** (haematological dissemination) is typical with the dissemination of multiple „millet seed„ sized nodules. In the advanced stage, a coarsely granular appearance is detected, caused by the merging of nodules (**snowstorm pattern**). Active (post-primary) tuberculosis can manifest itself in a variety of abnormalities on the chest X-ray. Consolidations (in nodular form) and patchy (mottled) shadowings (infiltrates) and/or cavities are often seen in the upper lungs with or without mediastinal or hilar lymphadenopathy. This includes **tuberculoma**, creating a homogeneous and well-defined shadow on the chest X-ray that needs to be distinguished from a lung tumour. Differential diagnosis problems can also be caused by **TB pneumonia**, in which clinical and X-ray picture is similar to other pneumonia with pneumonic infiltrate in the range of the lung segment or lobe. All late-diagnosed or poorly treated forms of tuberculosis can result in the development of **cavitary lesions** (caverns). Calcifications may be present. Rare forms of **TB pulmonary fibrosis** occur in the elderly and are characterized by induration, streaky fibrosis and deformative changes in the position of the mediastinum or other related organs. **TB pleuritis** most often occurs as a one-sided process; homogeneous pleural shading (effusion) is present in the X-ray image.

Laboratory (microbiological) diagnosis is much more important than in other respiratory infections. The basic precondition for reliable **evidence of mycobacteria**, and thus

confirmation of the aetiology of the disease, is the correct collection of material for microbiological examination. Material (sputum, puncture, etc.) is collected in a sterile container (prevention of contamination), and it should be collected before starting treatment. Direct **classical microbiological diagnostics** consists of the basic examination of biological material **microscopically** and **by culture**; in the case of positivity follows species identification and determination of sensitivity to antituberculotic drugs.

Microscopic examination (**Ziehl-Neelsen** staining suitable for the detection of acid- and alcohol-fast bacilli – AAFB) is a basic diagnostic method that takes only a few hours to perform. However, the analytical sensitivity is very low: the presence of at least 100,000 mycobacteria in 1 mL is necessary for a positive finding of acid-resistant bacteria in the biological material. However, microscopy only informs about their morphological properties and number, but not about their species affiliation and viability. It is suitable for the rapid diagnosis of lung tuberculosis with cavitary lesions.

Sputum culture is a highly specific test with 100-fold higher analytical sensitivity because it theoretically allows the multiplication of any, even a single, viable cell to the size of a macrocolony. Sputum cultures require special media (e.g., Löwenstein-Jensen medium), and the tubercle bacillus grows slowly, taking 4-7 weeks to give a positive culture and a further three weeks for in vitro testing of antituberculotic (AT) drugs sensitivity. The complete evaluation of the culture test includes the exact species specification of the cultured mycobacteria, as well as the determination of sensitivity to AT. All types of biological material intended for the isolation of mycobacteria (sputum, laryngeal swab, lavages, urine, bioptic material, cerebrospinal liquor, etc.) are examined by culture if they meet the criteria for proper collection.

Accelerated culture procedures are semi-automated or automated **radiometric culture systems** (**Bactec**) based on the detection of metabolic products of viable mycobacteria. In the culture medium, palmitic acid is present, labelled with the isotope carbon ^{14}C, which is metabolized to $^{14}CO_2$ in the presence of live mycobacteria. They can capture the initial phase of mycobacterial growth; we have a positive result in an average of 9 to 14 days. They suitably complement the classical culture method, which should always be established, and its implementation remains the gold standard for proving a case of disease.

Molecular genetic techniques use the creation of stable hybrids between the nucleic acids (RNA or DNA) of the mycobacteria in the sample under investigation and the specific

labelled gene probes. **Polymerase chain reaction** (PCR) techniques are very sensitive, and the presence of 1 mycobacterium in 1 ml of material is sufficient for the positivity of the examined sample. However, the technique is not able to distinguish whether the DNA comes from alive or already killed mycobacteria.

Endoscopic examination (bronchoscopy) followed by bacteriological and cytological or histological examination is indicated according to the finding. The examination does not need to be performed on everyone. It is fully indicated if a perforation of the node into the bronchial tree is suspected or if a bronchoalveolar lavage fluid is required to be examined.

Histological examination is an important diagnostic examination if it is possible to obtain representative material from different tissue structures in suspected infection. The examination is most often used in the diagnosis of extrapulmonary organ tuberculosis, which requires surgery. At present, it is regaining importance in resection of pulmonary treatment, especially in multidrug-resistant tuberculosis.

Tuberculin sensitivity – **the tuberculin skin test** was historically the first and, for the last few decades, also the only way to monitor TB infection. **Tuberculin** is a purified protein derivative (PPD) of the organism (mycobacterium tuberculosis). In the **Mantoux (II) test**, 0.1 mL of tuberculin solution is injected **intradermally** into the forearm. The response is a response of CD4 + T cells that have previously been sensitized with *M. tuberculosis* antigens (during infection, but also with BCG vaccination). The test is read in **72 hours**. Induration in two planes is assessed, and erythema is not considered. The positive reaction is greater than 5 mm (6 and more). Tuberculin positivity is an immunological response that distinguishes infected and uninfected individuals. However, the **search for infected individuals according to tuberculin positivity is practically impossible** in the vaccinated population by **routine vaccination** (in contrast to countries where they do not routinely vaccinate). In the vaccinated population, the reaction above 16 mm is hyperergic and may be post-infectious (after natural infection with virulent mycobacteria and usually lasts a lifetime) and post-vaccination (after vaccination, lasting about five years). However, a positive tuberculin test is not an indicator of immunity to TB and should not be used to evaluate the effect of vaccination! Conversely, the **lack of response to tuberculin does not rule out TB infection**. The tuberculin response decreases or disappears in advanced forms of tuberculosis, in the early stages of military tuberculosis, in treatment with corticoids and immunosuppressants, during severe fever and other diseases.

Latent tuberculosis infection (Latent TB) affects about 1/3 of the world population and is another source of TB disease, especially in the weakening of the body's defences (immunosuppression). It is the situation when a patient has been infected with *M. tuberculosis* at some time in the past but does not currently have active disease. The standard diagnostic procedure for patients with latent tuberculosis has included and still includes a clinical, radiological, bacteriological, and histological examination. People with latent TB are asymptomatic and usually have a normal chest X-ray. The Mantoux II tuberculin skin test is also included. Interpretation of the tuberculin test is complicated by post-vaccination immunity (BCG vaccination). The specificity and sensitivity of the test for post-vaccination immunity are low. The tuberculin test may have a false negative result, e.g., after overcoming viral infection, immunosuppressive and corticosteroid treatment, or in patients with HIV infection. Therefore, in vitro diagnostic laboratory immunological tests, called **IGRA tests** (***Interferon Gamma Release Assay Tests***), are currently used to diagnose latent TB infection. These are based on the detection of interferon gamma (IFN-γ) production by sensitized T cells exposed to *M. tuberculosis*. Two detection systems are used, QuantiFERON – TB Gold test or T-SPOT TB test. T cells from human whole blood are incubated in contact with ESAT-6 and CFP-10 antigens or TB 7.7, respectively. Incubation is followed by the detection of IFN-γ, which is produced when T-lymphocytes, as memory immune cells (with previous contact with the mycobacterium tuberculosis), recognize these antigens. These antigens are missing in the genome of all BCG vaccine strains, and extensive studies have shown that they are not present in most other *Mycobacterium species*. The test is exceptional, especially for its simple interpretation – positivity means the presence of specific memory T-cell clones in the circulation, and thus the presence of replicating *M. tuberculosis*. The absence of ESAT-6 or CFP-10 antigen in the BCG vaccine can be used in the diagnosis of active as well as latent tuberculosis in the population vaccinated with BCG – the **test result is not affected by vaccination**. In the diagnosis of latent tuberculosis infection, blood testing with an immunological IGRA test is **the method of choice**. Its sensitivity is estimated at 89% and specificity at 98%. However, the IGRA tests are most useful in the diagnosis of latent TB infection and **should not be used as a routine diagnostic tool for active tuberculosis**.

TREATMENT

The aim of treatment is to cure the patient, prevent late sequelae and death, prevent relapse of the disease, and prevent the transmission of tuberculosis to people who have been or are in contact with the patient. Antituberculotic drugs (anti-TB agents) have three different proportions: bactericidal capacity, environmental sterilization ability and the ability to prevent the development of mycobacterial resistance. Of the approved drugs, the **first-line** anti-TB agents that form the core of treatment regimens are **isoniazid** (INH, H), **rifampicin** (RIF, R), **pyrazinamide** (PZA, Z), **ethambutol** (EMB, E) and **streptomycin** (STM, S). First-line drugs are first administered and are usually chosen due to fewer side effects (shown in Table 8.1.) and higher clinical effectiveness. **Second-line drugs** are used when first-line drugs show no effect on the disease or when it is difficult to continue the treatment owing to the side effects. These drugs are the TB drugs that are used for the treatment of **drug-resistant TB**. The second-line drugs include, e.g., **levofloxacin, moxifloxacin, ofloxacin, clarithromycin, bedaquiline, delamanid** and **linezolid**.

Short-term treatment regimens requiring the use of bactericidal antituberculotic drugs are currently used. Isoniazid and rifampicin are the strongest bactericidal drugs acting against all populations of *Mycobacterium tuberculosis*. Isoniazid is the most effective drug acting on metabolically active bacilli, which can destroy mycobacteria in 90% within seven days. Rifampicin acts mainly on rapidly multiplying bacilli. It can destroy the so-called persistors, i.e., bacilli that remain inactive for a long time and have only intermittent metabolic periods. Pyrazinamide is effective in an acidic environment, especially against mycobacteria in macrophages, streptomycin acts mainly against bacteria in the extracellular environment, and ethambutol is particularly effective in combination with previous drugs in preventing the development of drug resistance as a bacteriostatic antituberculotic drug. Streptomycin is initially less used because it is administered parenterally (mostly as an intramuscular injection). **Anti-TB treatment must be combined to prevent the development of mycobacterial resistance** to antituberculotic drugs. The effectiveness of regimens in which INH, RIF and PZA are used as a basis is due to the rapid sterilization of the sputum and the low percentage of disease relapses. The combination of INH, RIF, PZA, and EMB, possibly also with streptomycin, achieves 90% negativity of the sputum already at the end of the second month of treatment. After six months of treatment, 95% efficacy of treatment without relapses was found. In view of this, in cases of newly diagnosed (for the first time in a person) TB (regardless of microscopic positivity or negativity), a **6-month treatment regimen with a 2-month initial**

phase in a four-dose combination (INH, RIF, PZA, EMB) and a **4-month follow-up phase in dual combination (INH, RIF)**. However, in patients with recurrent disease, extensive chest X-ray findings, or reduced risk of drug toxicity, if necessary, treatment regimens should be adjusted as recommended.

Before starting treatment, it is necessary to consider the type of TB case and which regimen we recommend to the patient – **case definition**. The optimal administration of drugs according to the appropriate schedule is daily. According to the WHO, supervised administration three times a week (in the follow-up phase or in HIV-negative in the initial and follow-up phases) is also acceptable, although a higher dose may be required for some medicines. The recommended dosage of drugs in the daily administration and the main side effects are shown in Tab. 8.1.

Table 8.1. The recommended dosage of first-line antituberculosis drugs

Drug	*Effect*	*Dose (mg/kg)*	*Side effect*
Isoniazid (H)	bactericidal	5 (max. 300 mg daily)	hepatotoxicity, neuropathy
Rifampicin (R)	bactericidal	10 (max. 600 mg daily)	hepatotoxicity, rashes, enzyme induction
Pyrazinamide (Z)	bactericidal	25	hepatotoxicity, rashes, elevated uric acid
Ethambutol (E)	bacteriostatic	15	optic neuritis
Streptomycin (S)	bactericidal	15 (> 60-year 10 mg/kg)	ototoxicity

The addition of **systemic corticosteroids** (prednisone, methylprednisolone) to antituberculotic treatment is indicated in forms of TB with marked exudation, especially in TB meningitis, in TB of all serous membranes – especially in exudative TB pleuritis. Furthermore, it is reserved for severe forms of TB as well as adrenal TB to prevent destructive changes in the parenchyma.

Early diagnosis of **tuberculosis during pregnancy** is very important not only from the point of view of the mother but also from the point of view of the child. The untreated disease

carries a high risk for both mother and child. If no clinical signs are present, a chest X-ray for the diagnosis should be postponed until the 12th week of pregnancy. The treatment of TB in pregnant women is not fundamentally different from the treatment of non-pregnant women; mostly, 4-combinations of antituberculotic drugs are used. The duration of treatment is not modified by pregnancy; active tuberculosis diagnosed at the time of delivery is also treated, and at the same time, isolation of the mother and newborn is necessary.

Treatment of extrapulmonary tuberculosis. Anti-TB treatment is the mainstay in the management of extrapulmonary TB. Treatment regimens may be similar to pulmonary TB, but it is appropriate to consider the specifics of each indication. For example, in the case of TB meningitis, the ability of anti-TB drugs to cross the blood-brain barrier must also be taken into account. While isoniazid, pyrazinamide, and cycloserine penetrate well into CSF, ethambutol and p-aminosalicylic acid have poor or no penetration. Rifampicin, streptomycin, and kanamycin penetrate the CSF well only in the presence of meningeal inflammation. A combination of intravenous rifampicin and moxifloxacin can be useful in this indication. **The duration of anti-TB therapy may be prolonged to 12 months in extrapulmonary TB**. **Extrapulmonary TB sometimes requires surgery**, such as drainage or thoracocentesis in extensive pleurisy, or in the case of urogenital TB, nephrectomy or ureteral reconstruction in post-inflammatory strictures may be indicated.

***Treatment of infected persons with resistant strains of tuberculosis*.** The rapid development of resistance to antituberculotic drugs currently administered is adversely affecting the development of tuberculosis infection worldwide. It is estimated that there are currently 50 million people in the world infected with multidrug-resistant strains of Mycobacterium tuberculosis. Resistance in newly diagnosed diseases – **primary –** refers to resistant strains of Mycobacterium tuberculosis secreted by newly diagnosed individuals who have never been treated with antituberculosis drugs or whose treatment has lasted less than one month. **Acquired** (secondary) resistance affects patients treated with antituberculotic drugs for at least one month. Primary resistance is less common. The most common causes of acquired resistance are incorrect choice or dosage of drugs, insufficient control of treatment, non-compliance with the treatment regimen by the patient or an increase in at-risk populations (homeless, drug addicts, prisoners, migrants, starvation, and malnutrition in developing countries).

According to the WHO recommendation, strains of Mycobacterium tuberculosis are referred to as:

• **Monoresistant** – with resistance to one of the basic antituberculosis drugs

• **Polyresistant** – with resistance to two or more antituberculosis drugs

• **Multidrug-resistant** (MDR-TB) – resistant at least to the combination of isoniazid and rifampicin

• **Extensive drug resistance** (XDR-TB) is a new concept introduced by the WHO in 2006. It is an isoniazid and rifampicin-resistant strain, as well as three drugs from six classes of second-line antituberculosis drugs. In practice, this means that the secreted tuberculosis bacilli are resistant to most currently known and used antituberculosis drugs.

In resistant tuberculosis, second-line drugs are used for the treatment. Criteria important for application, such as patient acceptability, tolerance, and potential toxicity, should be considered when selecting treatment for resistant forms of TB. In the therapeutic regimen, the patient should be administered at least as many sensitive drugs as the patient is resistant to, as recommended by the WHO.

Preventive chemotherapy (chemoprophylaxis) is an effective short-term passive protection used in the Slovak Republic in the control of tuberculosis for more than half a century.

Chemoprophylaxis can be divided into:

a. **Primary** – protection of a healthy or potentially infected individual from infection

b. **Secondary** – protection of an infected individual without clinical symptoms (with latent TB infection) from a clinically manifest form of TB.

The oldest preventive treatment used was **isoniazid** at a dose of 5 mg/kg per day for six months. Shorter regimens (3 months) are based on a combination with rifampicin as an alternative to isoniazid in the treatment of latent tuberculosis infection.

BCG VACCINATION

Bacillus Calmette-Guerin (BCG) live attenuated vaccine provides about 75% protection against tuberculosis for about 15 years. The vaccine is administered strictly intradermally in the attachment of deltoid muscle on the left shoulder at a dose of 0.05 ml horizontally, parallel to the surface of the skin. The response to BCG is like that of the primary complex, thus inducing a response in the lymph nodes. The effect of the BCG vaccine is based on the presumed close agreement of the biological properties of the BCG vaccine strain with the pathogenic M. tuberculosis strain, which leads to the induction of cross-immunological reactivity. The BCG vaccine does not normally cause disease in humans. It is used as a mechanism to improve the body's defences against tuberculosis. Because BCG is a lyophilized live vaccine, it cannot be used to prevent tuberculosis in HIV-infected individuals, in people suffering from other forms of immunosuppression, or in pregnant women, due to the potential risk of BCG infection. The effect of BCG in adults is variable, but infants and young children are protected from severe forms of tuberculosis, such as basilary meningitis or miliary tuberculosis. It is likely that active BCG immunization will not result in protection against *M. tuberculosis* infection but rather in the modulation of the immunological reactivity of the individual and the entire human population. Until 2012, widespread vaccination with the BCG vaccine was mandatory in the Slovak Republic. In many countries, including Slovakia, **widespread primary vaccination against tuberculosis has been stopped** (due to side effects- e.g., reactions at the site of the injection, swollen lymph nodes or abscess,) **and this has been limited to children in risk groups** (in our country in areas that are outbreaks with a high incidence of tuberculosis). However, data in European countries and experience in Slovakia show that discontinuation of BCG primary vaccination has resulted in an increase in the incidence of TB and other mycobacterial diseases in children.

NON-TUBERCULOSIS MYCOBACTERIA INFECTION

Non-tuberculous mycobacteria (NTM) are species other than those belonging to the *Mycobacterium tuberculosis complex* and do not cause leprosy. NTM are found in nature and the surrounding environment. There are about 140 species (e.g. *Mycobacterium xenopi, M. kansasii, M. abscessus, M. marinum*) which can cause a wide range of mycobacterial infections, with pulmonary infections being the most frequent (65-90%). Unlike tuberculosis, the source

of infection in NTBs is often not the infected individual but the environment (e, g. soil, water, animals, food). Individuals with reduced immunity are susceptible to NTB infection (immunosuppression due to Human immunodeficiency virus-HIV infection or corticosteroid use**). Diagnosis is based on clinical and radiological findings of infection, appropriate exclusion of other diagnoses and positive cultivation from at least two separate sputum samples** (or bronchial lavage, biopsy). **Interesting in the treatment is the fact that larger NTB mycobacteria are resistant to common anti-TB drugs**. The treatment is, therefore, a combination of antibiotics and anti-TB drugs (e.g., macrolides, aminoglycosides, amikacin, cefoxitin, rifampicin, ethambutol, isoniazid) and the duration of the treatment often exceeds 12 months.

9 RESPIRATORY INSUFFICIENCY

Respiratory insufficiency

- Respiratory insufficiency is the **inability of the respiratory system to maintain an adequate supply of oxygen to the tissues and may be accompanied by insufficient elimination of carbon dioxide**
- According to aetiology, respiratory insufficiency can be **acute** or **chronic**. Chronic respiratory insufficiency can be acutely worsened by the exacerbation of the underlying disease or sudden condition
- In prolonged respiratory failure, **compensatory mechanisms** develop to maintain homeostasis; these include tachypnoea, tachycardia, polycythaemia, and retention of bicarbonates
- A typical example of acute respiratory insufficiency is acute respiratory distress syndrome (ARDS)
- Chronic respiratory insufficiency develops in many respiratory diseases, such as COPD, pulmonary fibrosis, or hypoventilation syndrome
- Diagnosis depends on the evaluation of arterial blood gases
- The treatment of respiratory failure requires **treatment of the underlying disease** and sometimes the addition of **oxygen therapy, invasive and non-invasive ventilation**

DEFINITION

Respiratory insufficiency is defined by the inability of the respiratory system to maintain an adequate supply of oxygen to arterial blood, which may be accompanied by insufficient elimination of carbon dioxide from the blood. The diagnosis is not clinical but based on arterial gas assessment: $PaO_2 < 8,0$ kPa (60 mmHg) and/or $PaCO_2 > 6,0$ (45 mmHg). These values were arbitrarily set, and they are not rigid but serve as a general guide with consideration of patients' history and clinical evaluation.

AETIOLOGY AND PATHOGENESIS

There are several approaches to classifying respiratory failure.

Classification depending on the pathophysiologic mechanisms:

- **Type 1 or hypoxemic or partial respiratory insufficiency** is characterized by isolated hypoxemia in arterial blood

- **Type 2 or hypercapnic or global respiratory insufficiency** is characterized by hypoxemia coupled with hypercapnia in arterial blood.

The respiratory system consists of two parts. The lung performs gas exchange, and the pump ventilates the lung. The pump includes a chest wall with respiratory muscles and the respiratory controllers in the central nervous system linked to respiratory muscles through spinal and peripheral nerves. In respiratory insufficiency, there is a malfunction in one or both systems, i.e., oxygenation of mixed venous blood and/or carbon dioxide elimination.

Lung failure can be interpreted as gas exchange failure and is primarily manifested by hypoxemia. Oxygen passively diffuses from the alveolus to the capillary blood. An oxygen molecule passes through the alveolar and capillary walls and through the plasma membrane of a red blood cell to combine with a haemoglobin molecule. Naturally, diffusion of both oxygen and carbon dioxide happens within 0,25 seconds. This is a third of the total transit time of red blood cells through pulmonary circulation in normal lungs. In exercise, this total transit time drops to 0,25 seconds. Thus, in conditions like ILDs, which impair diffusion by increasing alveolar-capillary membrane thickness, there is a typical drop of PaO_2 during exercise. Carbon dioxide in the blood is excreted by diffusion across the alveolar membrane, and this process is more efficient than oxygen diffusion. That is why respiratory diseases impairing oxygen diffusion, unless very severe, do not affect carbon dioxide excretion.

Pump failure, i.e., ventilatory failure, results in hypoventilation manifested by both hypoxemia and hypercapnia. Hypoxemia is typically the first change to occur, while hypercapnia develops with some latency. Hypercapnia is seldom isolated but always couples with hypoxemia. The only clinical situation when we observe normoxaemia and hypercapnia is when a hypoventilating patient is breathing air enriched with a high fraction of oxygen. Oxygen relieves hypoxemia to some degree but does not suppress hypercapnia.

Hypoxemia is the finding present in both lung and pump failure. There are four pathological mechanisms responsible for hypoxemia that can be summarized:

- **Local ventilation/perfusion** (V´/Q') ratio inequalities

- **Shunt** – venous blood passing through non-ventilated parts of lungs or vascular shunt directly to the left atrium

- **Diffusion impairment** – thickening of the alveolar-capillary membrane

- **Local or global hypoventilation**

A disease resulting in respiratory insufficiency can present with one or more of the mechanisms mentioned above. For example, in COPD, all the factors may be present due to the

unevenly distributed closure of distal airways, ventilation/perfusion inequalities, areas of local hypoventilation and impaired diffusion. In pulmonary fibrosis, there is definite diffusion impairment, sometimes accompanied by ventilation/perfusion inequalities. In obesity hypoventilation syndrome, the basis of respiratory insufficiency is global hypoventilation, but there can also be impaired ventilation/perfusion ratio, mainly in the basal parts of the lungs. Also, a condition with hypoxemic respiratory insufficiency can lead to hypercapnia by putting an excessive load of work on respiratory muscles and their eventual exhaustion compared to the oxygen requirement results in hypoventilation.

Classification depending on the duration:

- **Acute respiratory failure**
- **Chronic respiratory failure**
- **Acute-on-chronic respiratory failure**

All these types can be both hypoxemic and hypercapnic. Acute respiratory failure may be life-threatening in clinical presentation. Chronic respiratory insufficiency is usually clinically indolent to unapparent due to mechanisms of compensation for respiratory acidosis.

Acute respiratory failure can develop in a few minutes to hours. The critical limit of PaO_2 decrease is 6,7 kPa (50 mmHg), which is not correctible by increasing oxygen concentration in inhaled air over 50%. The portion of the oxygen in inhaled air is called the fraction of inspired oxygen or FiO_2; in-room air FiO_2 is 21%. It can be increased mechanically by supplementing oxygen in a low-flow conventional manner, high-flow oxygen device (high-flow nasal cannula) or ventilator. A handy parameter to assess the severity of acute respiratory failure is the P/F ratio (also called PaO_2/FiO_2 ratio, Horowitz index, Carrico index) which is calculated as the ratio of PaO_2 (in mmHg) to fractional inspired oxygen (expressed as a fraction, not percentage). At sea level, the average P/F ratio is approximately 400-500 mmHg (55-65 kPa). P/F ratio below 300 mmHg indicates significant respiration impairment, usually related to acute lung injury (ALI). Further decrease in P/F ratio below 200 mmHg fulfils the criteria for acute respiratory distress syndrome (ARDS) and is associated with a significant likelihood of the need for invasive ventilation.

Acute hypercapnic respiratory failure may be the result of CNS depression, functional or mechanical defects of the chest wall, an imbalance of energy demand and supplies of the respiratory muscles, or adaptation of central controllers to prevent respiratory muscle injury and avoid fatigue. The critical level of $PaCO_2$ depends on the pre-existing condition of

the patient. For example, in acute poisoning with drugs suppressing the respiratory centre, $PaCO_2$ 6,0 kPa is already significant.

Chronic hypoxemic respiratory insufficiency is a result of mostly impaired gas diffusion and ventilation/perfusion mismatch. A typical example is interstitial lung diseases, where deposition of collagen hinders diffusion of oxygen while carbon dioxide can escape to alveolar air up until the terminal phases of the disease when muscle exhaustion triggers terminal hypoventilation.

Chronic hypercapnic respiratory insufficiency results from a prolonged pump or ventilatory failure, which can have multiple causes. Some diseases can present with both types of chronic respiratory insufficiency, for example, COPD.

Acute-on-chronic respiratory failure may ensue in diseases characterised by chronic respiratory insufficiency when there is a sudden worsening of the condition. This sudden deterioration of the condition may follow the natural behaviour of the disease in the form of an exacerbation, like in asthma, COPD, or pulmonary fibrosis. Alternatively, it can result from acute exhaustion of hitherto effective compensatory mechanisms, for example, acute pneumonia in a patient with COPD or decompensation of heart failure in patients with obesity hypoventilation syndrome.

Examples of causes of respiratory insufficiency are listed in Table 9.1.

Table 9.1. Examples of causes of respiratory failure

Acute hypoxemic respiratory failure
Severe lobar pneumonia, interstitial pneumonia, cardiogenic and non-cardiogenic pulmonary oedema, pulmonary embolisms, ALI and ARDS, alveolar haemorrhage, atelectasis, pleural effusion, pneumothorax, exacerbation of asthma
Acute hypercapnic respiratory failure
Intoxication (opioids, sedatives), head trauma, encephalitis, spinal cord trauma, myelitis, tetanus, botulism, poliomyelitis, Guillain-Barré syndrome, organophosphate poisoning, chest wall trauma, upper airway obstruction, sepsis, circulatory shock
Chronic hypoxemic respiratory failure
Interstitial lung diseases, COPD, severe persistent asthma, chronic left heart failure
Chronic hypercapnic respiratory failure
CNS diseases, chronic use of drugs, amyotrophic lateral sclerosis, consequences of poliomyelitis, muscular dystrophies, chest wall diseases, COPD, OHS
Acute-on-chronic respiratory failure
Exacerbation of asthma, exacerbation of COPD, exacerbation of IPF, OHS, chest wall deformities, myasthenia gravis

Classification depending on the activation of compensatory mechanisms:

- **Compensated respiratory insufficiency**
- **Decompensated respiratory insufficiency**

Acute compensatory mechanisms are hyperventilation with tachypnoea and tachycardia. With a prolonged duration of respiratory insufficiency, more mechanisms depending on the type of respiratory insufficiency come forward. Chronic hypoxemia usually provokes polycythaemia. The most complex compensatory reaction is to correct chronic hypercapnia to avoid respiratory acidosis. Buffer systems are the first to be activated. Then, the kidney increases the secretion of H^+, K^+, Cl^-, and retains Na^+ and bicarbonates. In a strict sense, decompensated respiratory failure is hypercapnia with respiratory acidosis, when the concentration of bicarbonates is not sufficient to maintain physiological pH.

Classification depending on the timing of the clinical presentation:

- **Latent respiratory insufficiency**
- **Manifested respiratory insufficiency**

Mainly in diseases with chronic hypoxemic respiratory insufficiency, the first signs may be inconspicuous. The patient has hypoxemia only after physical effort. That is called latent respiratory insufficiency. Manifested respiratory insufficiency is characterised by blood gases pathology also in resting conditions.

DIAGNOSIS

Clinical features

Hypoxemia induces hyperventilation by stimulating the chemoreceptors. Activation of the sympathetic nervous system manifests as **tachycardia**, often with **palpitations**, **tachypnoea**, **anxiety,** and **sweating**. Worsening hypoxemia impacts mental abilities; the patient is **confused**. Next, circulatory instability ensues, initial arterial hypertension is followed by hypotension and initial tachycardia switches to **bradycardia**. Severe hypoxemia damages vital organs (myocardium, brain) by ischemia. No matter the initial cause of hypoxemia, ventilatory failure may accede with hypercapnia and CNS suppression.

Hypercapnia manifests by sleepiness that can be replaced by **irritability**, **tremor**, and **headaches**. Central cyanosis is common. Hypercapnia causes vasodilatation. A patient may present with **blue mask syndrome** (oedematous face, cyanosis, glossy eyes, red conjunctiva). Severe hypercapnia induces **hypercapnic coma**.

Investigations

In **history**, the examiner must focus on the dyspnoea, its duration, presence of stridor, wheezing, orthopnoea, intoxication, and trauma. In chronic respiratory insufficiency, the subjective aspect of dyspnoea does not match up to the severity of blood gases changes.

Objectively, we observe cyanosis, and auscultation may reveal rales, crackles, wheezes, or very attenuated breathing.

Radiologic findings reflect the underlying pathology, like pneumonia, pulmonary oedema, pleural effusion, pneumothorax, and cardiomegaly. Conversely, in obstructive diseases or pulmonary embolism, radiologic findings can be discreet.

If the patient is clinically stable and can perform **pulmonary function tests**, they can reveal obstructive or restrictive ventilatory impairment.

Other valuable diagnostic procedures include ECG, echocardiography, laboratory cardiology markers (natriuretic peptide, D-dimers, troponins), pulmonary angiography, and microbiologic, neurologic and toxicologic examination.

Arterial blood gases (ABGs) are the standard of the examination and are necessary to establish respiratory failure diagnosis properly. Arterialised capillary blood gases are a potential replacement if there is no option to extract arterial blood, but the reliability is slightly inferior. The parameters we consider are partial pressures of gases (PaO_2, $PaCO_2$), acid-base balance (pH), and metabolic compensation (bicarbonates HCO_3^-, base excess BE). Monitoring oxygen saturation can also be a useful non-invasive tool.

Understanding arterial blood gases

Interpretation of findings in arterial blood gases may often be challenging for students and young doctors.

Normal body metabolism leads to acid production, such as lactic acid, phosphoric acid, and sulphuric acid. Control of the body's pH is called acid-base balance. Lungs, kidneys, and buffers control this balance. Arterial blood gas tests are used to assess acid-base balance in patients. $PaCO_2$ represents acidifying component and HCO_3^- is the basic component. Physiological values are summarised in Table 9.2.

Table 9.2. Physiological values of arterial blood gases and acid-base balance

pH in arterial blood	7.35-7.45
PaO_2	10-13.3 kPa (75 – 100 mmHg)
$PaCO_2$	4.5-6 kPa (34 – 45 mmHg)
HCO_3^-	22-26 mmol/L
BE	-2.5 to + 2.5 mmol/L

There are four main types of acid-base imbalance. The complexity of the topic exceeds the scale of this textbook. A comprehensive overview is provided in Table 9.3.

Table 9.3. Patterns and causes of acid-base imbalance

Imbalance	Finding	Example
Respiratory acidosis	↓ pH	Type 2 respiratory failure
	↑ $PaCO_2$	
	↑ HCO_3^-	
	positive BE	
Respiratory alkalosis	↑ pH	Hyperventilation Pulmonary embolism Mechanical ventilation
	↓ $PaCO_2$	
	↓ HCO_3^-	
	normal BE	
Metabolic acidosis	↓ pH	Ketoacidosis Renal failure Lactic acidosis Diarrhoea
	↓ $PaCO_2$	
	↓ HCO_3^-	
	negative BE	
Metabolic alkalosis	↑ pH	Vomiting Diuretics
	↑ or normal $PaCO_2$	
	↑ HCO_3^-	
	positive BE	

To provide a better comprehension of the acid-base imbalance, here are some examples with explanations:

Example 1:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.4	10.5	4.5	25

These are physiological values of ABGs.

Example 2:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.4	6.5	3.5	22

The patient is hypoxemic. At the same time, hypocapnia indicates hyperventilation. The concentration of bicarbonates is slightly decreased, but still, in the physiological range, we conclude there has not been enough time to compensate for the decrease of $PaCO_2$. So, we

might suppose some acute respiratory condition eliciting respiratory distress, perhaps pneumonia, exacerbation of asthma or pulmonary embolism.

Example 3:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.5	12	3.5	22

The patient is normoxemic but hypocapnic with respiratory alkalosis. We can suppose there is hyperventilation of short duration with no sufficient compensatory mechanisms. These ABGs might be expected in a patient with respiratory distress inhaling oxygen or in a healthy person undergoing hysteria.

Example 4:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.4	6.5	4.5	25

This patient has hypoxemia but no signs of hyperventilation or hypoventilation. It can be part of various diseases, either chronic (e.g., IPF, COPD) or acute (e.g., pneumonia).

Example 5:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.4	6.5	9.0	35

This patient is both hypoxemic and hypercapnic. However, pH is in the normal range as the concentration of bicarbonates is elevated. Probably, the compensatory mechanisms have been active for some time. This is an example of ABGs of a patient with chronic hypoventilation, e.g., in obesity hypoventilation syndrome or COPD.

Example 6:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.3	5.0	10.0	33

In this case, there is respiratory acidosis. The patient is both hypoxemic and hypercapnic. The hypoventilation has been present for long enough to retain an excessive number of bicarbonates. However, the concentration of bicarbonates is still not enough to prevent the development of acidosis. This suggests that the patient suffers from chronic hypoventilation that has been exacerbated, as is typical in acute-on-chronic hypercapnic

respiratory failure and can be seen in COPD exacerbation or decompensation of obesity hypoventilation syndrome.

Example 7:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.25	5.5	9.0	23

In this case, the hypoxemic patient is hypoventilating, as indicated by high $PaCO_2$, but the reaction of retaining bicarbonates has not yet taken place. Thus, the pH relays respiratory acidosis. The absence of reaction on the part of bicarbonates suggests either their acute consumption or rather acute accumulation of $PaCO_2$. Diagnostic procedures to evaluate potential causes of acute hypercapnic respiratory failure should be invoked.

Example 8:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.4	9.0	5.8	28

This patient is slightly hypoxemic; $PaCO_2$ is still in the normal range but attacking the upper limit. The increased concentration of bicarbonates suggests there has been some hypoventilation lately. pH is normal. This type of ABG can be seen in patients with nocturnal hypoventilation; during the day, CO_2 is eliminated sufficiently, but its nocturnal accumulation provokes retention of HCO_3^-.

Example 9:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.25	10	11	30

In the case of this respiratory acidosis, we observe severe hypercapnia. Elevation of bicarbonates indicates that hypoventilation has been present. Nevertheless, oxemia is abnormally “good” for this degree of hypoventilation, suggesting the patient has been/ is inhaling oxygen in high concentration. Inhaling oxygen in a hypoventilating patient may further deepen hypoventilation, promote retention of CO_2 and respiratory acidosis, and is not routinely recommended at a high flow rate.

Example 10:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
7.1	6.5	9	18

This patient is both hypoxemic and hypercapnic; therefore, he is hypoventilating. Respiratory acidosis might be expected, but the current pH is disproportionately low when considering $PaCO_2$, and the concentration of bicarbonates is also decreased. This suggests that apart from hypoventilation, there is also some metabolic cause of acidosis which should be addressed.

Example 11:

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)	HCO_3^- (mmol/L)
6.8	9.0	2.5	8

In this case, we present severe acidosis with mild hypoxemia and pronounced hypocapnia; the concentration of bicarbonates is severely decreased. This is metabolic acidosis, possibly due to ketoacidosis in diabetes Type 1.

TREATMENT OF RESPIRATORY FAILURE

The basis of therapy for respiratory insufficiency is to treat the underlying disease. Often this cannot be done, as the patient may suffer from progressive disease. Therefore, respiratory insufficiency is corrected to prevent further hypoxaemic organ damage and to improve subjective symptoms.

Oxygen therapy

Acute oxygen therapy is used to improve oxygen delivery in cardiac and respiratory arrest situations, severe acute hypotension, in the presence of metabolic acidosis, pneumothorax, and when saturation of oxygen is measured by pulse oximetry (SpO_2) is below 90%. In acutely ill patients, oxygen therapy is recommended to keep SpO_2 in the range of 94-98%. However, in patients with chronic hypoventilation where oxygen therapy may cause ventilatory decompensation (severe COPD, neuromuscular disorders, obesity hypoventilation syndrome), the target SpO_2 should be 88-92%. If oxygen therapy fails to achieve the target SpO_2 without progressive hypercapnia and acidosis, ventilatory support should be added.

Oxygen may be delivered by nasal cannula, simple oxygen mask, special Venturi mask or high-concentration reservoir mask (non-rebreather mask).

The flow rate in a standard **low-flow oxygen system** generates a flow of oxygen up to 15 L/min. The fraction of inspired oxygen (FiO_2) obtained using these devices depends on the patient's breathing pattern, peak inspiratory flow rate, delivery system and mask characteristics. The devices cannot heat and effectively humidify gas at higher flow, which limits their use. Also, if a patient has a high inspiratory rate, the amount of entrained room air dilutes the oxygen, resulting in lowering FiO_2.

Lately, as an alternative to standard oxygen devices, **high-flow nasal oxygen therapy (HFNO)** has been used. A blender of air/oxygen is connected via an active humidifier to a nasal cannula and allows FiO_2 adjustment independently from the flow rate. The mixed gas flow rate reaches up to 60-80 L/min. The oxygen flow rate can reach 60 L/min, and FiO_2 can be as high as almost 100%. HFNO has the advantage of better comfort and tolerance of the patient. By providing small positive end-expiratory pressure (PEEP) to combat intrinsic alveolar PEEP, it increases tidal volume, and decreases dyspnoea and respiratory rate. This modality is used in acute hypoxemic respiratory failure to improve oxygenation pre-intubation and treat patients after surgery or extubation. Its effectiveness has also been demonstrated in pandemic pneumonia. It has been suggested that it may also be used in acute hypercapnic respiratory failure as it washes out alveolar air and keeps a favourable arterial-alveolar gradient for the diffusion of CO_2, thus evading potential CO_2 retention. This, however, needs to be confirmed by large-scale studies.

Long-term oxygen therapy (LTOT) is used in patients with chronic hypoxemic respiratory insufficiency. It can also be added to non-invasive ventilation for patients with chronic hypercapnic respiratory insufficiency. In COPD patients, LTOT increases survival, reduces polycythaemia, protects against the development of pulmonary hypertension, and may improve sleep quality and neuropsychiatric symptoms. The prescription of LTOT requires fulfilment of criteria:

- $PaO_2 < 7{,}3$ kPa on room air
- $PaO_2 < 8{,}0$ kPa on room air in addition to pulmonary hypertension, secondary polycythaemia, right heart failure, or nocturnal desaturation

In LTOT, oxygen can be delivered by a home concentrator or portable concentrator, although a compressed oxygen cylinder or liquid oxygen is also an option. The patient is usually recommended to use LTOT for 16-18 hours per day, and the flow rate depends on blood gases.

Non-invasive ventilation

Non-invasive ventilation (NIV) is the provision of ventilatory assistance without the use of an invasive airway. NIV may be provided as either positive pressure via a facial mask, mouthpiece, or a helmet. Because the whole system patient-ventilator is not hermetically closed, there are expected leaks of air to the environment. NIV with negative pressure, e.g., via a tank ventilator, cuirass or pneumojacket, is not routinely used. Hence, we will concentrate on NIV providing positive pressure. In the strict sense, NIV uses two levels of positive pressure (i.e., bilevel positive airway pressure or BiPAP, as mentioned in the chapter about sleep apnoea). In the broader sense, continuous positive airway pressure (CPAP) might be called a type of NIV as it uses the same interface, and most machines providing BiPAP also provide CPAP mode. However, in this place, we will use NIV and BiPAP interchangeably. NIV can be volume-preset or pressure-preset. In volume-preset NIV, a certain amount of volume is delivered to the lungs with no regard to the intensity of pressure; this is a useful but potentially damaging mode. Pressure-preset ventilators are more widely used. They use two levels of pressure in different portions of the breathing cycle: expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP). The difference between the two establishes the pressure support, which aids inspiration and decreases the work of breathing by unloading the respiratory muscles. This increases tidal volume, minute ventilation, and improved gas exchange. EPAP at the same time, keeps airways patent, eliminates obstructive apnoeic episodes, and counters intrinsic end-expiratory pressure (e.g., in COPD), thus improving ventilation/perfusion balance. Newer NIV machines include software enabling to regulate the pressures according to the patient's specific need, either in terms of eliminating apnoeic pauses or providing required tidal volume, which is variable in different body positions or course of the disease.

NIV is indicated in patients with acute hypercapnic respiratory failure, notably decompensated, i.e., in respiratory acidosis. The typical examples are acute exacerbation of COPD, acute hypercapnic respiratory failure in neuromuscular and chest wall diseases, in obesity hypoventilation syndrome. It often fails in acute hypoxemic respiratory failure. An exception is cardiogenic pulmonary oedema, where CPAP is recommended in the presence of normocapnia.

Long-term NIV is used in patients with chronic hypercapnic respiratory insufficiency, supplemented by oxygen therapy if necessary. The devices contain software enabling to check patient's compliance and effectiveness of ventilation on various parameters.

Invasive ventilation

Invasive ventilation is usually provided in an intensive care unit. It delivers ventilatory support via orotracheal/nasotracheal intubation cannula or tracheostomy. There are supposed to be no air leaks from the system. The principle of invasive ventilation is the same as in NIV, but the nomenclature differs. PEEP is positive end-expiratory pressure which is technically the same as EPAP or CPAP. However, by circumventing collapsible parts of airways via intubation or tracheostomy, PEEP may be decreased. IPAP is not preset. Instead, pressure support (PS), i.e., the difference between two pressures, is determined. Unlike NIV, FiO_2 can also be adjusted up to 100% if needed. Invasive ventilation allows much higher pressures than NIV, and the patients are sedated to tolerate them and relieve respiratory distress and load of work for respiratory muscles. The lungs mechanics must be frequently checked, and the ventilator settings adjusted to avoid iatrogenic lung injury.

Invasive ventilation aims to achieve the highest possible saturation with the lowest possible FiO_2 and recruit collapsed alveoli.

The indication of invasive ventilation is in acute respiratory failure not responding to oxygen therapy or NIV. The classic example of a clinical situation requiring invasive ventilation is **ARDS** which is an acute inflammatory pulmonary disease as a result of systemic damage (e.g., shock, sepsis, polytrauma) or local damage (severe pneumonia, lung contusion or aspiration of gastric acid). Pathophysiologically, it is characterised by interstitial oedema, alveolar exudate, increased permeability of the alveolar-capillary membrane, multiple atelectasis, vasoconstriction, infiltration of neutrophils and high cytokine activity. The beginning is sudden. Acute hypoxemic respiratory failure develops where oxygen saturation does not respond adequately to increased FiO_2 in supplemental oxygen therapy. A decrease in the P/F ratio is one of the indicators to recommend invasive ventilation. Despite all accessible and complex care, ARDS has high mortality of 25-70%.

Chronic invasive ventilation can also be dispensed at home in identical indications to NIV when the patient cannot use a face mask. It is usually provided via tracheostomy and bears a risk of iatrogenic infection.

Attached figures

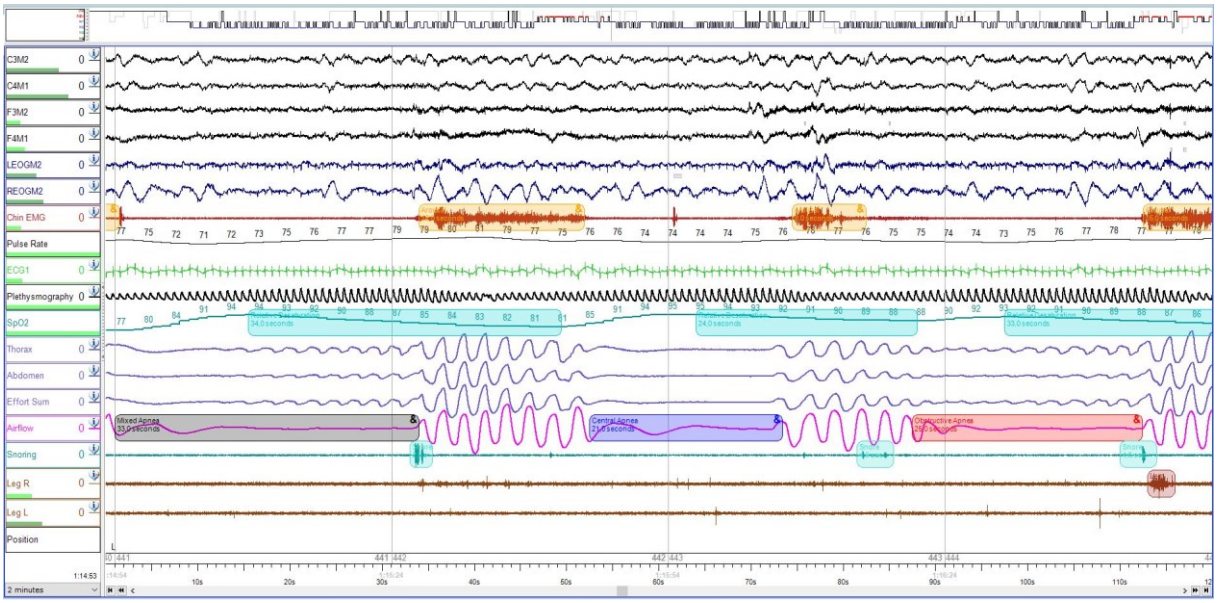


Figure 6.1. Polysomnographic recording – an excerpt of 2 minutes. Channels shown are from top to bottom: hypnogram, EEG (4 channels), EOG (2 channels), chin EMG, pulse rate, ECG, plethysmographic recording of pulse amplitude, oxygen saturation, respiratory effort (thoracic, abdominal, and combined), oronasal airflow, snoring, EMG of anterior tibial muscles and body position.
The red box indicates the obstructive apnoeic episode – the respiratory effort is present.
The blue box indicates the central apnoeic episode – the respiratory effort is absent.
The black box indicates the mixed apnoeic episode – initially, the respiratory effort is absent; later, it resumes.
Light blue boxes indicate desaturations – a decrease in oxygen saturation.
Orange boxes indicate arousal – shift in EEG activity.

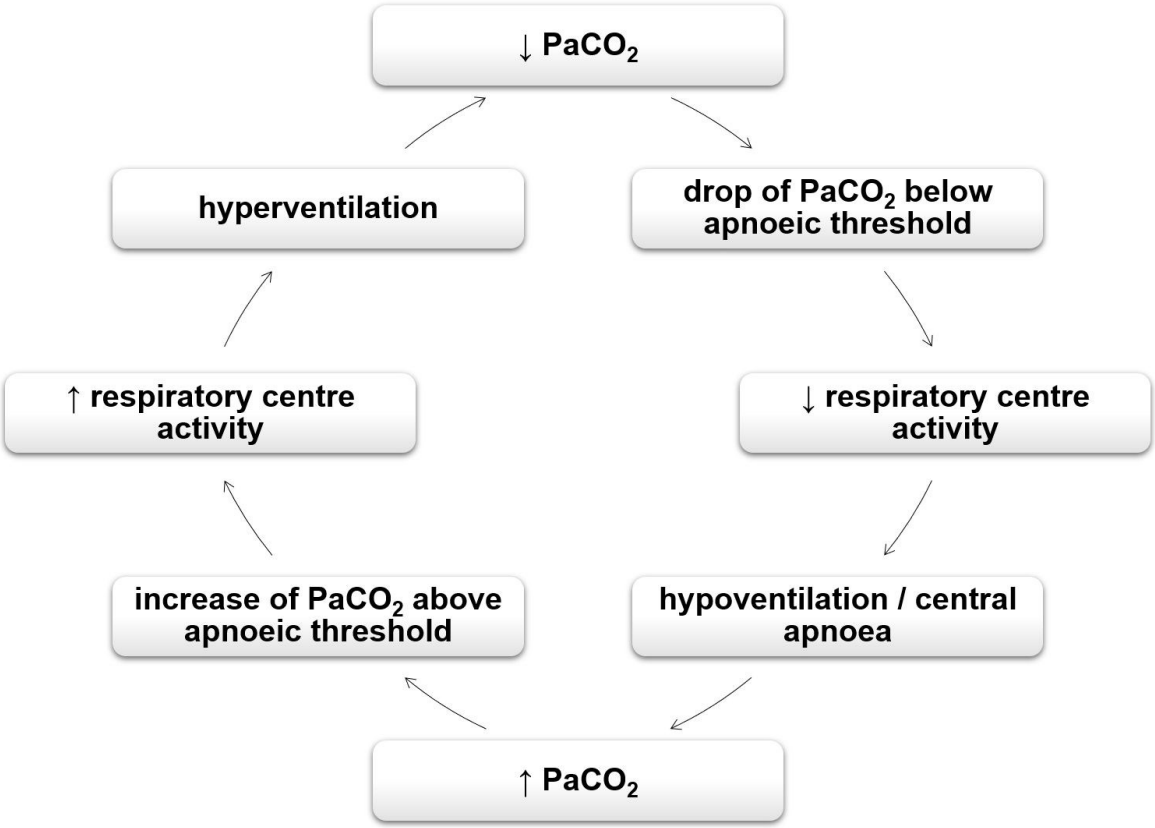


Figure 6.2. The vicious cycle of repetitive hyperventilation and hypoventilation/central apnoea due to the instability of ventilatory drive and shifted apnoea threshold

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