Management of cough in adults – recommendations for family physicians

Magdalena Szwaj, MD

Cough definition

A cough is natural, defensive and desirable reflex which provides clearance of secretions and prevents the lower airways from the aspiration of foreign bodies.

A cough is a physiological reflex of a defensive nature, which serves to clear the respiratory tract of excess secretions, dust, gases and/or foreign bodies. The essence of the cough reflex is a deep inhalation, followed by a phase of air compression and then a rapid exhalation with an open glottis.

A cough may be conscious or reflexive. The stimulus to trigger the cough reflex is the irritation of mechanoreceptors located in the respiratory tract and lungs (foreign body, smooth muscle spasm or edema of the bronchial mucosa) or chemoreceptors (chemical compounds, inflammatory mediators). The cough reflex may also be generated by stimuli outside the lung, aroused by irritation of the esophagus,irritation of the pharyngeal wall or external auditory canal (via the vagus nerve)

Chronic cough, lasting especially more than 8 week is a significant problem for patients and it is a common cause of looking for medical advice from various medical specialists. The persistent cough causes perception of discomfort by patients, disorders of other organs and reduces quality of life. The complex etiology of chronic cough in some situations can lead to difficulties with recognition a cause of persistent cough. The diagnosis of long-lasting cough occasionally needs interdisciplinary cooperation of different medical specialties. This article describes basic etiological and clinical aspects of chronic cough and gives simple advices how to diagnose and treat patients whit this symptom.

-In clinical practice, various cough classification systems are used. The most important is the division of cough based on its duration.

-The importance of the presented division results from numerous observations indicating that the relative frequency of occurrence of various causes of cough very clearly depends on its duration.

-Depending on sputum production, cough can be divided into **productive** and **dry.**

In the past, attempts were made to assign productive and dry cough to individual disease entities, but in practice it turned out that the accuracy of such associations is quite limited, and a given disease entity may manifest itself with a cough of various natures. Nevertheless, a number of features are used in the differential diagnosis of the causes of cough, including the time of day or night at which the cough occurs, the circumstances provoking the cough, and coexisting symptoms. The most complete characterization of the cough is of great diagnostic importance, e.g. a chronic, dry cough occurring at night may suggest asthma, especially if it is accompanied by other symptoms, e.g. wheezing. An acute cough, changing its character from dry to expectorant (in the presence of other symptoms, e.g. fever, headaches) is typical of acute upper respiratory tract infections (URTIs).

• Acute cough (<3 weeks):

- URTI = Upper respiratory tract infections (VIRAL)
- exacerbation of underlying disease (COPD, asthma)
- acute bronchitis, allergy;
- less often: aspiration, pulmonary embolism, pulmonary edema, pneumonia, foreign body in the respiratory tract, irritating dusts and gases.

• Sub-acute (3-8weeks)

Subacute cough is most often, in up to 90% of cases, of post-infectious origin.

- **bronchitis**
- **pneumonia**
- **pertussis**
- **rhinitis and sinusitis**
- **asthma**
- **gastroesophageal reflux**
- **bronchitis (non-asthmatic eosinophilic or exacerbation of chronic bronchitis)**

-Post infection cough (including TB)

-Upper Airway Cough Syndrome

• Chronic (>8 weeks)

often: • asthma • chronic bronchitis, COPD • gastroesophageal reflux • upper respiratory tract diseases (including URTI) • medications (especially ACEI)

less often: • bronchiectasis • irritants (tobacco smoke, marijuana, occupational and environmental factors) • lung cancer and other neoplastic diseases of the chest • non-asthmatic eosinophilic bronchitis • post-infectious cough • circulatory system diseases (e.g. left ventricular heart failure, arrhythmias)

rare: • interstitial lung diseases • sarcoidosis • tuberculosis • bronchiolitis • pulmonary embolism • vascular inflammatory diseases• foreign body • upper gastrointestinal tract diseases (esophagitis, habitual aspiration) • irritation of the external auditory canal • vocal cord dysfunction• psychogenic cough• idiopathic cough

1. URTI

By URTI we mean inflammation of the middle ear, nose and sinuses, throat, larynx and trachea. The disease is mainly caused by viruses (80-90% of cases), among which the following predominate: **rhinoviruses, adenoviruses, coronaviruses, influenza and parainfluenza viruses, RS virus and enteroviruses.** Acute bacterial infections of the upper respiratory tract constitute a negligible percentage of non-hospital infections. Full-blown acute URD infections occur 2-5 times a year in adults and 7-10 times in children. Most of them, especially in patients not burdened with other coexisting chronic diseases, have a mild and self-limiting course. The basic symptoms include: nasal discharge (of various types – from watery to thick, mucous), often accompanied by nasal obstruction, sore or irritated throat, sneezing, hoarseness, headaches, a feeling of general malaise, increased body temperature or moderately enlarged lymph nodes in the neck may occur. Cough accompanies UOD infection in 40–50% of cases. An exception is infections with influenza and parainfluenza viruses, in which cough occurs in over 90% of patients. Initially, it is dry, non-productive, and then evolves, most often towards a moist, productive cough. Cough associated with UOD usually lasts no longer than 2 weeks. The diagnosis is made on the basis of the collected history and physical examination, taking into account the assessment of UOD. No additional tests are required. Most UOD infections do not require treatment; symptomatic treatment is sometimes used. In patients with very severe, dry cough, especially nocturnal, the use of antitussive drugs may be considered: levodropropizine, dextromethorphan, butamirate, first-generation antihistamines, possibly with pseudoephedrine (off-label use). Codeine is less and less frequently recommended due to its numerous side effects (addiction, inhibition of the respiratory center), and its use should be limited only to adult patients.

Despite the lack of clear evidence based on high-quality clinical studies, muco- and secretolytic drugs (bromhexine, ambroxol, acetylcysteine, carbocysteine, erdosteine, phytotherapeutics, hypertonic NaCl solution in inhalations). When using these preparations, remember to dose them correctly, as well as to properly hydrate the patient. Combining mucolytics and secretolytics with antitussives is also controversial and is not recommended.

Most acute UDO infections are of viral etiology, which is why there are usually no indications for antibiotic therapy. Antibiotic treatment should be considered in patients with clear indications of the possibility of bacterial infection, with chronic diseases, and with immune disorders. Unjustified use of antibiotics in acute respiratory infections significantly contributes to the spread of multidrug-resistant bacteria

2. Acute bronchitis

Acute bronchitis (AB) is a mild and usually self-limiting infection of the lower respiratory tract. Detection of the etiological agent of AB is difficult, but the most common cause of this disease is considered to be viral infections (responsible for about 90% of all AB cases).

The remaining 10% of cases have a bacterial etiology, mainly Mycoplasma pneumoniae, Chlamydophila pneumoniae, Bordetella pertussis and B. parapertussis. It is unlikely that other bacterial pathogens are the primary cause of AB in previously healthy individuals. In the adult population, the most common viruses detected in the course of bronchitis are human respiratory syncytial virus (HRSV), metapneumovirus, parainfluenza viruses 1, 3, and 4, and bocavirus type 1. During the epidemic season, the number of cases of bronchitis caused by influenza A and B viruses increases significantly. Cough is the dominant symptom of acute bronchitis. Depending on the course and phase of the disease, it can be dry or productive. The nature of the expectorated secretion can be diverse – from mucous to purulent. Contrary to popular belief, purulent appearance of sputum is not characteristic of bacterial infections, but is also found in viral infections. It is not easy to distinguish between cough caused by bronchitis and cough in the course of other acute infections, e.g. rhinitis and sinusitis. A typical feature of OZO is a longer period of cough (1–3 weeks).

Fever is not a typical symptom of AB and its presence requires differentiation from pneumonia.

In practice, differentiating between the two most common causes of cough, i.e. bronchitis and asthma,may be difficult. This applies in particular to patients in whom the diagnosis of asthma has not been previously established. Sometimes, it is only after several or a dozen episodes of recurrent cough, shortness of breath and wheezing, which are initially treatedas episodes of acute bronchitis, that the suspicion of asthma is raised. The latter may be supported by: atopy, positive family history, symptoms accompanying cough: wheezing and shortness of breath,especially at night, recurring episodes of cough and wheezing outside the typical periods of respiratory tract infections(e.g. during the summer), association of symptoms with allergen exposure.Treatment of bronchitis is primarily symptomatic

3. Pneumonia

Pneumonia (P) is a severe form of infection of the lower respiratory tract, usually of bacterial etiology in adults. The most common pathogen
causing community-acquired pneumonia is Streptococcus pneumoniae (13–31%), less frequently other bacteria: Haemophilus influenzae (3–7%), Staphylococcus aureus (1–4%) and Moraxella catharallis (1–2%).

Atypical microorganisms also play an important role: Mycoplasma pneumoniae (7.2%), Chlamydophila pneumoniae (4.3%) and Legionella pneumophila (2.8%). Other important causes include respiratory viruses (4–16%), especially HRSV and parainfluenza viruses, and in the epidemic season, influenza viruses. Mixed etiology is much rarer in adults than in children (5%). In various studies, the share of individual pathogens in the etiology shows differences
Cough is the dominant clinical symptom of PE, however, similarly to the course of OZO, it has a varied and variable character depending on the etiology
and the period of the disease. It may be accompanied by fever,
shortness of breath, chest pain.

Pneumonia of atypical etiology often has a poor course of symptoms, the cough may be moderately intense, non-productive. The diagnosis of PE can usually be established based on subjective and objective symptoms, however, in doubtful cases, additional tests play an important role,
primarily a chest X-ray, determination of CRP concentration (assessment of the risk of a severe course) or procalcitonin in serum (test unavailable in primary care).

Antibiotic therapy for non-hospital pneumonia is empirical in nature, and the basis for choosing the drug
is knowledge of the most common etiological factors

4. PERTUSISS

In adults, Bordetella pertussis infection is responsible for approximately 3% of cases of prolonged cough. During the course of infection, massive damage to the respiratory epithelium occurs. Clinical criteria for the diagnosis of the disease in adults include a cough that persists for more than 2 weeks without any other cause, which meets at least one of the following conditions: it is paroxysmal, leads to vomiting or is accompanied by a loud inspiratory whistling sound ("foaming"). In the initial period of infection (catarrhal phase, 1–2 weeks), the cough is mild and is accompanied by nonspecific flu-like symptoms.

Nocturnal attacks of dry cough precede the development of the second period of infection (paroxysmal cough phase, lasting 1–10 weeks), when a cough that meets the clinical criteria for the diagnosis of the disease predominates.
It is paroxysmal, occurs around the clock, but can be more severe at night. In this period of the disease, strong bronchial hyperresponsiveness is revealed, which is why coughing fits are provoked especially by inhaled irritants, changes in the temperature of the inhaled air or physical exertion. During the recovery period (2–3 weeks), symptoms ease, and the risk of other respiratory infections increases. In adults, coughing fits provoked by exertion may persist for many weeks. In the vaccinated population, symptoms of infection with the pertussis bacillus may be less typical [15]. Laboratory confirmation of the diagnosis requires molecular testing (rapid PCR test up to 4 weeks from the onset of symptoms), culture (up to 2 weeks) or serological testing (2–12 weeks). Given the commonness of the latter, it should be remembered that the diagnostic value is the presence of IgA antibodies, demonstration of seroconversion in the IgG class, or possibly IgM. There is no need for laboratory verification of the diagnosis in a person with typical symptoms, if it is known that they had contact with a patient in whom infection with the pertussis bacillus has been confirmed.

If the diagnosis is made within 2 weeks of the onset of symptoms, causal treatment with macrolide antibiotics should be started without fail. Such a procedure allows to shorten and alleviate the course of the disease, including cough. However, in adults, it is rarely possible to establish the diagnosis at this time. Diagnosis of the disease between the 2nd and 4th week is a relative indication for antibiotic therapy, because it does not affect the severity of symptoms, but limits the spread of infection.

The main method of prevention is vaccination. It does not provide lasting immunity, but reduces the risk of severe infection and complications. Booster vaccinations are recommended for adults in contact with newborns, infants and children (including healthcare workers), pregnant women (optimally the third trimester, 27–34 Hbd) and care home workers.

Nr/data w KSI 026 prac. diagn.: **5362** / 02-07-2024

Wynik bada specjalistycznych

Nazwa badania	Wynik badania	Zakres referencyjny
Materiał: Krew ylna, surowica, data i godz. pobrania: nie podano, data i godz. przyj cia: 02-07-2024		
Krztusiec - p/c IgM (Bordetella pertussis) (S09)	**1,3 Ratio**	
	pozytywny	<0,8 negatywny >=0,8 do <1,1 graniczny >=1,1 pozytywny

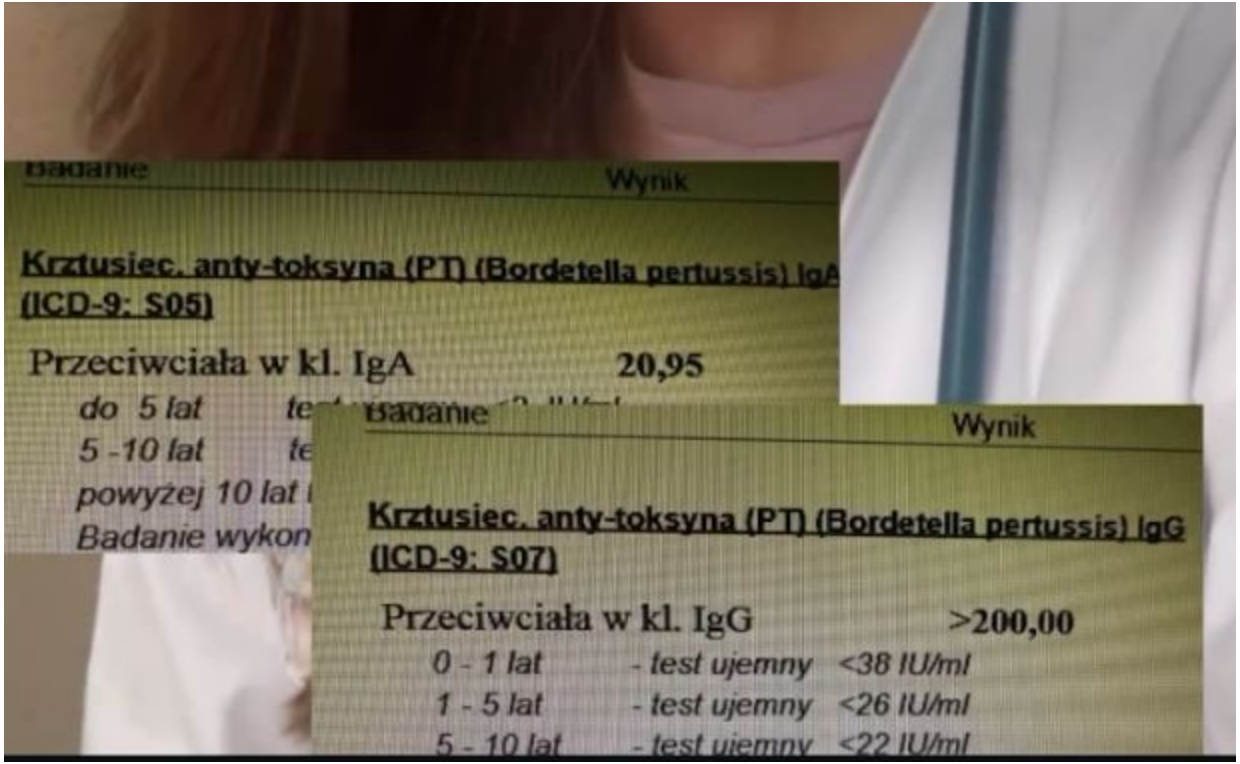
Badanie wykonano metod ELISA na analizatorze EuroLab Workstation, zestawem odczynnikowym firmy Euroimmun

Oznaczenie w surowicy przeciwciał IgG specyficznych dla bakterii Bordetella pertussi, wykorzystywane jest w diagnostyce k zaka na dróg oddechowych).
Przeciwciała IgM s przeciwciałami "wczesnej fazy" infekcji, a ich obecno mo e wiadczy o aktywnym zaka eniu.
Przeciwciała IgM s wykrywane przez 2-3 miesi ce od zaka enia, po czym zanikaj .
W okresie wykrywalno ci s najlepszym wska nikiem przebiegaj cej choroby u dorosłych nieszczepionych lub szczepionych poni ej 6 miesi ca ycia.

Nazwa badania	Wynik badania	Zakres referencyjny
Materiał: Krew ylna, surowica, data i godz. pobrania: nie podano, data i godz. przyj ci		
Krztusiec - p/c IgG (Bordetella pertussis) (S07)	**89,7 IU/ml**	
	rekomendowane powtórne badanie próbki pobranej pobranej ponownie po 7-10 dniach	>=100 IU/ml pozytywny <40 IU/ml negatywny >=40 - <100 IU/ml graniczny

Badanie wykonano metod ELISA na analizatorze EuroLab Workstation, zestawem odczynnikowym firmy Eu

Oznaczenie w surowicy przeciwciał IgG specyficznych dla bakterii Bordetella pertussi, wykorzystywane jest w zaka na dróg oddechowych).
Przeciwciała IgG s przeciwciałami pó nej fazy choroby, wskazuj cymi na rozwini cie humoralnej odpowiedzi chorobie w przeszło ci lub przebytym szczepieniu.


Badanie
Wynik
Krztusiec, anty-toksyna (PT) (Bordetella pertussis) IgA
(ICD-9: S05)
Przeciwciała w kl. IgA 20,95
do 5 lat
5 -10 lat
powyżej 10 lat
Badanie wykon
Badanie
Wynik
Krztusiec, anty-toksyna (PT) (Bordetella pertussis) IgG
(ICD-9: S07)
Przeciwciała w kl. IgG >200,00
0 - 1 lat - test ujemny <38 IU/ml
1 - 5 lat - test ujemny <26 IU/ml
5 - 10 lat - test ujemny <22 IU/ml

IgG, IgA….

Isolate the child for 5 days after starting antibiotic therapy

klabax --> bactrim

The increase in IgG level occurs in a larger percentage of infected people (over 90%) than the increase in IgA, however, IgA is a better marker of current infection in vaccinated people (over 2 years of age), because, as it is believed, they arise mainly (though not exclusively) as a result of natural infection. In unvaccinated children under 6 months, the presence of IgG indicates their maternal origin. Serological tests become diagnostically important in the late phase of whooping cough (i.e. after 2 weeks of illness, i.e. in the so-called paroxysmal phase), when bacteria become undetectable by PCR or microbiological culture methods) and lose significance in the period of 8-12 weeks, counting the appearance of cough, when the level of antibodies begins to be undetectable by routine methods. Ideally, serological tests should include two blood draws: in the acute phase of the disease and in the recovery phase and be based on the analysis of seroconversion. Seroconversion (increase in antibody concentration) from undetectable values is evidence of pertussis.

Subacute cough

The most typical example of patients with prolonged (subacute) cough, the cause of which is a previous acute respiratory infection, are patients with so-called **post-infectious cough (post-infectious bronchial hyperresponsiveness**). Diagnosis of post-infectious cough requires demonstrating a clear temporal relationship between the appearance of cough and respiratory infection

and ruling out pneumonia based on a chest X-ray. The cough subsides (usually spontaneously) within 8 weeks.

A smaller group of patients with subacute cough, but requiring much greater attention, are patients with chronic respiratory diseases, who report to a doctor in the first weeks after the onset of symptoms. Diagnosis of chronic respiratory diseases (e.g. pulmonary tuberculosis, COPD, asthma, lung cancer) at an early stage of their development is of paramount importance for the effectiveness of treatment. Therefore, in all patients with subacute cough, in whom the initial period of symptoms proceeded without other symptoms of acute respiratory tract infection, special diagnostic vigilance should be maintained.

CHRONIC COUGH- diagnosis

First, it is necessary to determine whether cough is an isolated symptom or whether it is accompanied by other symptoms, the coexistence of which may indicate the need for differential diagnosis. When diagnosing the causes of chronic cough, the following should be considered first and foremost:
• chronic bronchitis associated with cigarette smoking,
• occupational exposure to substances harmful to the respiratory system,
• the influence of medications (ACE-I, BETA-BLOCKERS, STATINS)- cough may occur in up to 15% of patients treated with ACEI, more often in women. It is often accompanied by tickling, scratching, itching in the throat. The coexistence of asthma is associated with an increased risk of cough in a patient treated with ACEI. Cough usually disappears within 1–4 weeks after discontinuing ACEI, at the latest after 3 months.
The method of treatment is to change the ACEI to a drug from another group (e.g. sartan)

It is very important to pay attention to whether, in addition to chronic cough, there are no so-called alarm symptoms, such as hemoptysis, dyspnea, chest pain, low-grade fever, weight loss, hoarseness, dysphagia. Their detection requires urgent diagnostics, often in hospital conditions.
The key role in determining the cause of chronic cough is played by the assessment of a **chest radiograph**. If the **X-ray** shows abnormalities in the respiratory system, further diagnostics depend on their nature. If the radiograph is normal, then the most common cause of chronic cough is one or more of the following diseases:

• asthma (including the cough variant) or nonasthmatic eosinophilic bronchitis (NAEB),
• upper respiratory tract cough syndrome (UACS), including chronic rhinitis (allergic and nonallergic), chronic sinusitis, gastroesophageal reflux (GERD)

Other causes of chronic cough should include chronic bronchitis, COPD, bronchiectasis, prolonged infections, lung cancer, interstitial lung disease, and circulatory system diseases If the above-mentioned causes are excluded,chronic idiopathic cough is diagnosed. However, if chronic cough persists despite correct treatment of the identified cause, difficult-to-treat cough should be diagnosed. In both cases, the cause of persistent cough may be hypersensitivity of the cough reflex (cough hypersensitivity syndrome)

MOST COMMON CAUSES OF PERSEVERE COUGH

- UACS (upper airway cough syndrome)
- asthma
- GERD (gastroesophageal reflux disease)
- The consequence of smoking may be the development of chronic obstructive pulmonary
- disease (COPD), chronic bronchitis and secondary pulmonary emphysema
- Other common causes of persistent cough include post-infectious bronchial hypersensitivity, lung cancer, interstitial lung diseases,
- complications of treatment with angiotensin-converting enzyme inhibitors, cystic fibrosis,
- chronic diseases of the paranasal sinuses
- psychogenic cough

When looking for the causes of chronic cough, it is worth remembering about clinical entities that may atypically manifest themselves with persistent cough. The most common atypical causes of persistent cough include:
— obstructive sleep apnea (OSA),
— snoring,
— hypothyroidism,
— congenital sensory polyneuropathy,
— cardiac arrhythmias (mainly premature ventricular contractions),
— left ventricular heart failure,
— chronic fungal infections,
— pharyngeal tonsil hypertrophy,
— cerumen blocking the external auditory canals.

One of the less common causes of cough is non-asthmatic eosinophilic bronchitis

From the point of view of a practicing physician, at the initial stage of searching for the causes of cough, the most important role is assigned to the **physical examination and subjective examination.** A detailed history, determination of the characteristic features of cough, knowledge of the factors that exacerbate or alleviate its occurrence and a properly conducted physical examination constitute the basis for further diagnostics, and often will allow for establishing a preliminary diagnosis.

At this stage of diagnostics, it is important to pay attention to the burden of nicotine and to the occurrence of symptoms suggesting extrapulmonary causes of cough, for example cardiac or neurological, which may require diagnostics specific to a given disorder. Next, a **chest X-ray** should be performed in each patient, in two projections: posterior-anterior (P-A) and lateral. A chest X-ray often reveals disorders that may be a potential cause of cough and — depending on the result — determines further diagnostic and therapeutic directions. In people whose symptoms may suggest the occurrence of upper respiratory tract cough syndrome, a detailed laryngological examination should be performed, allergic tests should be performed. In some cases, it is necessary to perform a **computer tomography of the sinuses** to search for the cause of the occurrence of upper respiratory tract pathology.

It often happens that the above tests are not conclusive, then the next step should be to perform functional tests of the respiratory system. **Spirometry** should be performed, and in the case of bronchial obstruction, also spirometry after inhalation of a bronchodilator. Further in-depth pulmonary diagnostics may include **whole-body plethysmography or a test of the diffusion ability of the lungs for carbon monoxide.** In the case of detection of disorders suggesting the occurrence of asthma, diagnosis may be aided by **peak expiratory flow (PEF) examination** in the form of average values calculated from two weeks of measurements, nonspecific or specific provocative tests, or demonstration of improvement in lung function after four weeks of anti-inflammatory treatment.

In the absence of diagnosis of typically pulmonary disorders, gastroesophageal reflux disease should be considered as one of the common causes of persistent cough. It is recommended to perform **24-hour monitoring of esophageal pH with measurement of esophageal impedance**, endoscopic examination of the upper gastrointestinal tract, and attempt treatment with high doses of proton pump inhibitors. If diagnostic imaging and lung function tests are normal, there is no bronchial hyperresponsiveness and an extrapulmonary cause of the cough has been excluded, consideration may be given to **collecting sputum to determine the eosinophil count and performing bacteriological tests** to exclude an infectious background, especially atypical or fungal.

A high-resolution computed tomography of the chest may be necessary in every person with chronic cough of unknown etiology. Before completing the diagnostic process, a **bronchofiberoscopy** examination should be performed in every patient without an established diagnosis.

1. SPIROMETRY

Among the tests available in primary care, spirometry should be mentioned. This is a rather difficult test, requiring effort and cooperation from the patient. Only properly performed spirometry ensures diagnostic reliability of the result.
The speed, intensity and duration of the exhalation maneuver, as well as the shape of the airflow curve and repeatability of individual measurements should be carefully monitored.

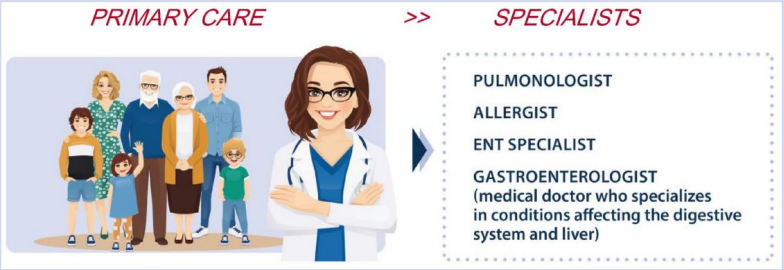
The basic criteria for assessing the correctness of the test are:
-the speed of the initial exhalation phase (BEV < 150 ml),
-time to PEF (tPEF < 0.3 s),
-exhalation duration (FET ≥ 6 s)
-and the presence of a plateau on the exhalation curve.

The obtained results should be assessed primarily in terms of standard deviation, and not as a percentage of the predicted value. This is especially important when assessing the type of ventilation disorders detected. The adoption of the FEV1/FVC index < 0.7 as a criterion for obstruction leads to its overdiagnosis in the elderly and insufficient sensitivity of the test in young people. It is recommended to assess the FEV1/FVC ratio relative to the lower limit of normal (LLN). Obtaining an FEV1/FVC value below LLN justifies the diagnosis of ventilation disorders of the obstructive type.

A diastolic test (standardly, salbutamol is administered inhaled at a dose of 400 µg) may be considered positive if the improvement in FEV1 or FVC is greater than 200 ml and exceeds 12% of the predicted value. It should be remembered that the degree of improvement must be related to the predicted value, not to the initial value of the index. The change in the FEV1/FVC index is of no significance in the interpretation of the diastolic test.

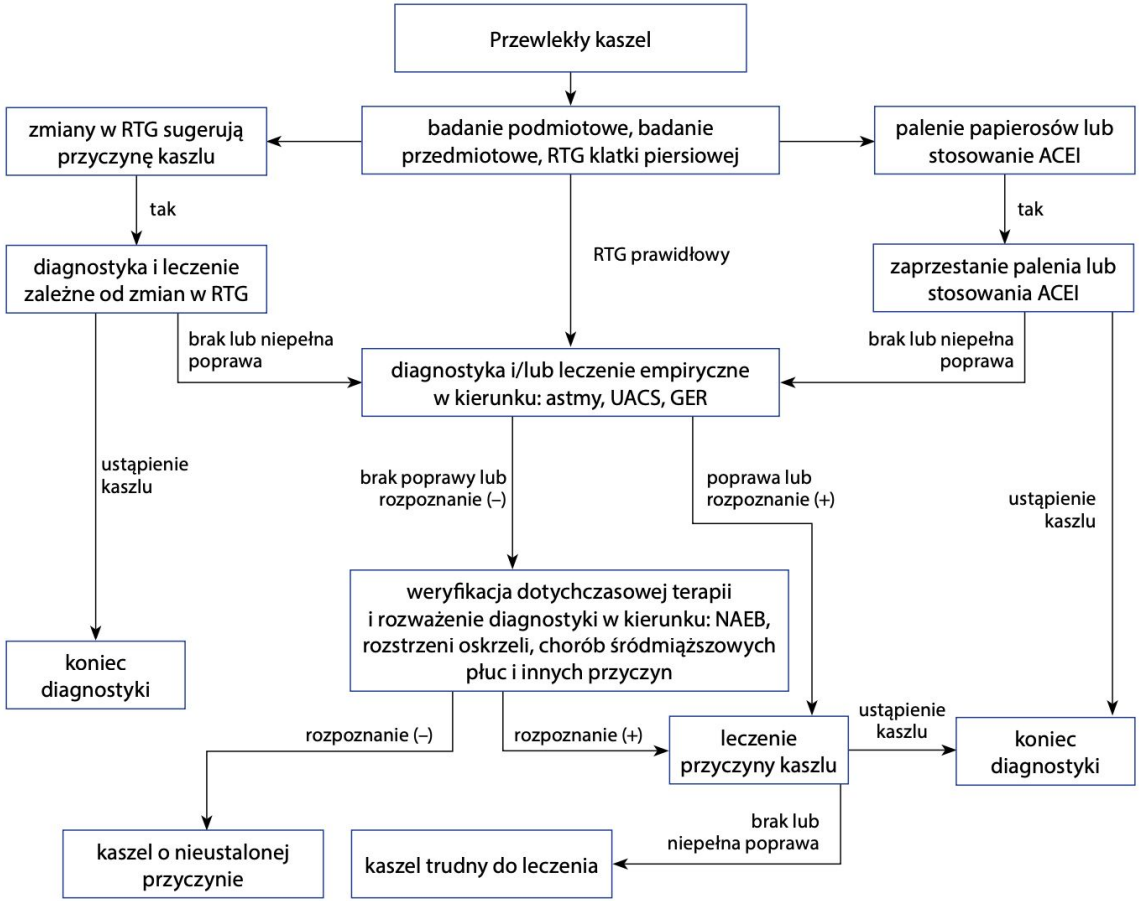
Table 4 contains the most important diagnostic tests required to confirm the diagnosis of the cause of cough. Some of the tests listed are only available as part of specialist diagnostics, so in some clinical situations it is possible to previously attempt empirical treatment, e.g. with inhaled glucocorticosteroids (IGS) or proton pump inhibitors (PPIs).

What did the specialists agree on regarding referring people with chronic cough from primary care?



Referral from primary care to other specialists in the following situations

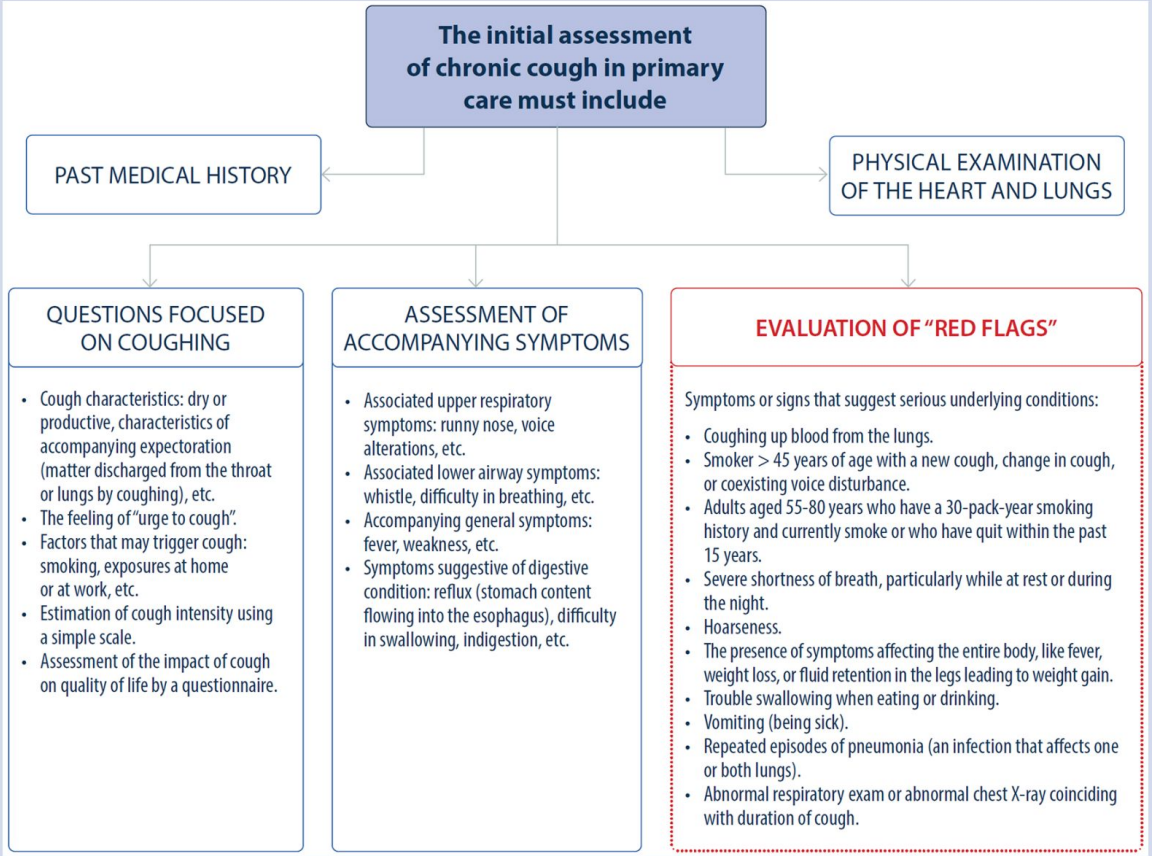
- → If there is a serious red flag that requires priority assessment without delay (e.g. spitting or coughing up blood, heavy smoking, weight loss, etc. -see figure in section 3-)
- → When, following a **primary care** investigation, no diagnosis has been found to justify the **chronic cough**.
- → To confirm a suspected diagnosis when complementary tests not available in the **primary care** setting are required (e.g. a computed tomography or CT scan: a diagnostic imaging procedure that uses a combination of X-rays and computer technology to produce images of the inside of the body).
- → To prescribe a treatment or perform a diagnostic intervention unavailable in **primary care**.
- → In case of refractory **chronic cough** (when a diagnosis has been found in **primary care**, the cause has been correctly treated, but the cough persists).
- → In case of suspected cough hypersensitivity syndrome (troublesome coughing that happens when exposed to low levels of things like heat or certain chemicals).

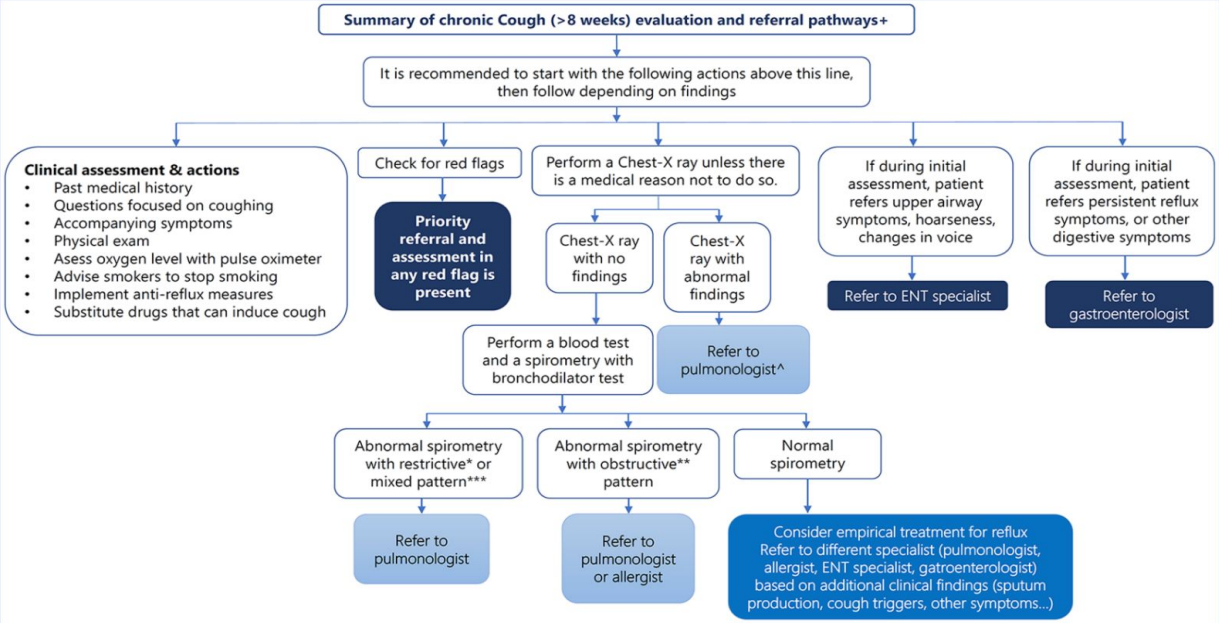


ACEI – inhibitory enzymu konwertującego angiotensynę, UACS – kaszel wywołany chorobami górnych dróg oddechowych, GER – refluks żołądkowo-przełykowy

Rycina 1. Algorytm postępowania diagnostycznego w kaszlu przewlekłym

3. *What did the physicians agree on regarding the initial assessment to be performed in **primary care** for people with **chronic cough**?*





+**Referral** to a specific specialist must not preclude **referral** to other specialists if different pathologies co-exist or are suspected in the same patient. **Referral** pathways are subjected to accessibility to each specialist in the different healthcare systems.

^Unless a diagnosis is reached and patient can be treated in **primary care**

*Restrictive pattern: means that lungs cannot inflate with the appropriate amount of air: lungs have lower volume capacity

**Obstructive pattern means that the air cannot circulate at appropriate speed in the respiratory system due to partial obstruction (e.g. spasm in the bronchial tube)

***Mixed pattern means a combination of restrictive and obstructive pattern.

ASTHMA

Asthma is estimated to cause approximately 24–29%
of cases of cough lasting longer than 8 weeks. Cough may be one of its symptoms (along with
shortness of breath, wheezing or a feeling of chest congestion – the classic form of asthma), but it may also be
the only symptom (cough variant of asthma).
A cough associated with asthma is most often dry or occurs with scanty expectoration of white-yellow sputum, usually occurs with changes in temperature or humidity, exposure to strong odors, exposure to smoke and occurs at night. Diagnosis of asthma as the cause of cough requires documentation of reversible bronchial obstruction in spirometry during a bronchodilator test and, if spirometry is normal, demonstration of airway flow variability by comparing successive spirometry readings or assessment of the diurnal variability of peak expiratory flow or demonstration of bronchial hyperresponsiveness in a bronchial provocation test (e.g. with methacholine) [10, 48]. A clear indication in favor of the diagnosis of asthma as the cause of cough is also the disappearance of this symptom
after the initial clinical diagnosis of asthma has been made and ICS has been used. The finding of an increased (> 3% of non-epithelial cells) percentage of eosinophils in induced sputum or an increased (> 30–40 ppb) concentration of nitric oxide in exhaled air (FeNO) (tests unavailable in primary care) may be of auxiliary importance in diagnosing asthma as
the cause of cough [49, 50]. The basic drugs used in the treatment of cough
being a symptom of asthma are ICS. Their effectiveness is high, but does not always reach 100%. In most patients, a combination of β2-mimetics and ICS is indicated (the latter are used in medium doses, and in the case of ineffectiveness – high doses)

Tabela 5. Leczenie zespołu kaszlu związanego z górnymi drogami oddechowymi (UACS)

Przyczyna		Leczenie – podstawowe zasady
przewlekłe zapalenie błony śluzowej nosa (*rhinitis*)	alergiczne	• donosowe glikokortykosteroidy • azelastyna z propionianem flutikazonu • leki przeciwhistaminowe: doustne, donosowe • ewentualnie montelukast
	niealergiczne	• donosowe glikokortykosteroidy • bromek ipratropium (niedostępny w Polsce jako pojedynczy lek w postaci donosowej) • inne metody wspomagające
rynopatie		• donosowe glikokortykosteroidy • bromek ipratropium • azelastyna z propionianem flutikazonu
przewlekłe zapalenie zatok przynosowych (*rhinosinusitis*)	z polipami	• donosowe glikokortykosteroidy (ewentualnie krótko – doustne glikokortykosteroidy) • w uzasadnionych przypadkach kwalifikacja do operacji
	bez polipów	• donosowe glikokortykosteroidy • w uzasadnionych przypadkach kwalifikacja do operacji
	w zaostrzeniach	• antybiotykoterapia
refluks żołądkowo-przełykowy		• inhibitory pompy protonowej • modyfikacja stylu żywienia, dieta, redukcja masy ciała
zespół nadwrażliwości kaszlowej (*cough hypersensitivity syndrome*)		patrz: *Zespół nadwrażliwości odruchu kaszlu, kaszel idiopatyczny*

Chronic bronchitis and chronic obstructive pulmonary disease

Chronic bronchitis associated with cigarette smoking is the most common cause of chronic cough, but paradoxically this symptom relatively rarely prompts patients to seek medical help. In some patients, cough occurs daily, but in others it may subside and recur.

It is usually accompanied by expectoration, which often
increases in the morning hours.
Chronic bronchitis can be diagnosed if the patient coughs and expectorates
most days of the week, for at least 3 months of the year,
for 2 consecutive years. Some patients are COPD patients, in whom cough is one of the three
main symptoms, along with expectoration and dyspnea on exertion. Although smoking is by far the most common factor inducing CAP or COPD, the cause of the disease may also be exposure to air pollution or harmful
factors present at home or in the work environment. The diagnosis of chronic bronchitis
is based on clinical symptoms, while
the diagnosis of COPD requires spirometry with a dilator test and confirmation of the persistence of obstruction in spirometry after bronchodilator therapy (most often
salbutamol) [52].

The basic treatment for cough associated with COPD and COPD is to stop smoking and avoid exposure to other harmful factors. The best intervention by a physician is advice and anti-smoking therapy. The drugs of choice in COPD patients
are bronchodilators, which affect, among other things,
reducing the intensity of cough. In stable COPD and COPD, antibiotics are not recommended, while
the use of mucolytic drugs may be beneficial [53, 54]. In exacerbation of COPD or COPD, both the introduction of
antibiotics and short-term use of systemic glucocorticosteroids may be justified

Pulmonary tuberculosis

In countries with a high incidence of tuberculosis, a cough
lasting more than 3 weeks requires consideration of its diagnosis. Poland is a country with a low incidence (the rate in 2017 was 15.1/
100,000 inhabitants), but in situations of increased risk of infection, it is necessary to consider tuberculosis in the differential diagnosis of the causes of cough.
Such situations include: contact with a person suffering from tuberculosis, staying in environments with an increased incidence (prisons, nursing homes), immune disorders, neoplastic diseases, chronic kidney disease, alcoholism, wasting.

Cough is a typical symptom of tuberculosis, but it rarely occurs as the only symptom. It is most often accompanied by, among others, hemoptysis, shortness of breath, weakness, subfebrile conditions, loss of appetite and body weight, and
night sweats. Initially, the cough may be dry,
but later it is usually accompanied by expectoration
of mucous or purulent sputum. Suspicion of tuberculosis requires immediate performance of a chest X-ray and sputum examination for the presence of acid-fast bacilli. In the case of
cough in the course of tuberculosis, it is necessary to apply effective antituberculosis treatment, according to the recommendations

GER

Before starting diagnostics for GER, other causes of chronic cough, such as asthma, rhinitis and sinusitis, and other diseases discussed above, should be excluded. There is no generally available test that could be considered the gold standard in the diagnosis of reflux-related cough. For this reason, a common element of diagnostic procedures is the empirical initiation of PPI therapy and the recommendation of lifestyle modifications aimed at reducing the frequency of lower esophageal sphincter relaxation. If the cough decreases or disappears during therapy, it should be concluded that it was related to GER.

The tests that are important in the diagnosis of GER-related cough include:

- esophageal pH-metry,

which allows determining the time of esophageal exposure to acid reflux. The limitations of the test include the lack of a parameter that would allow predicting the response to treatment and the inability to assess non-acid reflux.

Pharmacotherapy of cough

Pharmacological treatment of cough depends primarily on its nature **(dry or productive cough)**, and also indirectly on the cause. Below are described the drugs that are most often used in cough therapy.

Antitussive drugs
Drugs with central action - non-opioid
In addition to its central action, **butamirate** has a weak bronchodilator effect. Adverse symptoms occur rarely (0.5-1%) and include drowsiness, nausea, vomiting, diarrhea and skin rashes. The drug is registered for patients from 2 months of age.

Dextromethorphan - its mechanism of action involves inhibition of N-methyl-D-aspartate receptors activating calcium channels. The strength of the antitussive effect is slightly greater than codeine, and it is also better tolerated by patients. In recommended doses, it does not inhibit the respiratory center. In case of overdose, the depressive effect of the drug on the nervous system is emphasized. It interacts with opioids, alcohol and other drugs that worsen cognitive processes and respiratory drive and has addictive potential. In Poland, it is registered from the age of 6.

Centrally acting drugs - opioids
Codeine is a prodrug activated by the CYP2D6 enzyme system in the liver to morphine. It acts on opioid receptors in the cough center in the medulla oblongata. Like morphine, it can cause persistent constipation and addiction during long-term use. In case of overdose, it can also cause depression of the respiratory center, especially in small children and the elderly. Like dextromethorphan, it is used as a narcotic substance. It has been registered for use in children over 12 years of age, but according to the European Medicines Agency (EMEA), it should not be used in children under 18 years of age. Centrally acting antitussive drugs are associated with a greater risk of adverse effects on the nervous system than drugs acting peripherally. Particular attention should be paid to impaired psychomotor functions, including reduced ability to drive vehicles and increased risk of falls, especially in the elderly. The risk of interactions at the level of the central nervous system between the antitussive drugs listed in this subchapter and alcohol and other psychotropic substances (e.g. older generation antihistamines) should also be taken into account [99–103].

Peripherally acting drugs

Drugs with peripheral action include **levodropropizine, butylaminobenzoic acid esters and oxadiazole derivatives (e.g. oxolamine).** **Levodropropizine** is used in clinical practice.
Levodropropizine inhibits the activity of the cough reflex arc by blocking the secretion of neuropeptides from C-fiber endings and bronchoconstriction induced by histamine, serotonin and bradykinin. Controlled clinical trials have confirmed that levodropropizine is an effective antitussive drug that provides significantly better results compared to placebo [107] and centrally acting drugs [108, 109]. These studies have shown that levodropropizine significantly reduces the intensity and frequency of cough and nocturnal awakenings compared to codeine, coperastine and dextromethorphan.
The 2006 ACCP guidelines recommend the use of levodropropizine in adult patients with cough due to acute or chronic bronchitis for short-term symptom relief. These guidelines state that levodropropizine has the highest efficacy in relieving dry cough associated with lower respiratory tract infections compared with centrally acting drugs such as codeine or dextromethorphan.

Intestinal corticosteroids should not be routinely used in subacute cough (especially post-infectious), as there is insufficient evidence to confirm their efficacy [122]. Also, in idiopathic or refractory cough, there are no indications for the use of intestinal corticosteroids.

Secretolytics, mucolytics, mucokinetics – mucoactive drugs Under normal conditions, a small amount of mucus secreted into the lumen of the respiratory tract is unconsciously transported by the ciliated epithelium towards the larynx and then swallowed. Both acute and chronic respiratory diseases can cause hypersecretion of mucus and change its properties. When the amount and properties of mucus prevent its effective transport and removal by physiological means, a cough appears, which is supposed to support the transport of mucus from the lower to the upper respiratory tract, including the throat and oral cavity.

- **expectorants-** hypertonic NaCl solutions, essential oils
- **mucolytics-** erdosteine, NAC
- **mucokinetic drugs-** bronchodilators (mainly β2-agonists), tricyclic nucleotides, ambroxol.
- **mucoregulatory drugs-** Carbocisteine

Mucolytic drugs

The name mucolytic drugs suggests that they cause "lysis" of the components of mucus secreted into the respiratory tract. This is in fact the case, but the full definition is broader. Mucolytic drugs include all agents that, by changing the physicochemical properties of mucus by degrading the polymers of mucins, DNA, fibrin and F-actin contained therein, reduce the effusion of secretions in the respiratory tract

N-acetylcysteine (NAC) contains one free thiol group (SH) in its molecule, which, by reacting with disulfide bridges in the polymers of mucus glycoproteins, degrades the three-dimensional structure of mucus glycoproteins [114]. Such an effect is observed when the drug is administered by inhalation. There are serious doubts whether this mechanism is equally important when administered orally or intravenously. In addition, NAC has strong antioxidant and anti-inflammatory effects (including due to its antioxidant effect, inhibition of neutrophil and macrophage chemotaxis, and reduction of bacterial cell adhesion to the epithelium) .A limitation of chronic NAC use is the risk of adverse effects, the most important of which are gastrointestinal disorders. They may manifest as heartburn, dyspepsia, diarrhea, nausea, vomiting. Other possible adverse effects of NAC include watery rhinorrhoea, tinnitus, stomatitis, and allergic skin reactions.

Erdosteine is the newest mucolytic drug approved for marketing. It has several specific features that may be important for its efficacy and safety. It contains two sulfur atoms in the molecule, which are, however, bonded in a thiolactone ring and a sulfide bridge. Erdosteine is therefore a prodrug, the active metabolite of which (N-thiodiglycolylhomocysteine) containing a free thiol group is formed only after its absorption from the gastrointestinal tract and enzymatic degradation of the thiolactone ring in the liver [115]. Orally administered erdosteine does not cause degradation of gastric mucoproteins and is well tolerated.
Importantly, it is not contraindicated in patients with gastric and duodenal ulcers. Erdosteine has a strong antioxidant effect.
In vitro studies have shown that it is superior in this respect to other mucolytic drugs [116]. Similarly to NAC, erdosteine limits the adhesion of bacterial pathogens to epithelial cells. It also shows synergistic effects with numerous antibiotics, increasing their penetration into the respiratory tract secretions [117, 118]. The results of a recently published large, multi-center study indicate that in COPD patients, chronic treatment with erdosteine reduces the risk of exacerbations (by almost 20%), shortens their duration and reduces the use of temporarily used bronchodilators [54]. Importantly, the percentage of adverse events in the group of 215 patients using erdosteine for 12 months was low (only 3 cases related to the use of the drug) and did not differ from that observed in the group using placebo.
Due to its slightly different mechanism of action, carbocisteine has been discussed in the group of mucoregulatory drugs.