BRONCHIAL ASTHMA IN CHILDREN. Clinical presentation, diagnosis, treatment

Methodical elaborations for foreign students

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
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БРОНХІАЛЬНА АСТМА У ДІТЕЙ. Клініка, діагностика, лікування.

Методичні вказівки для студентів

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Asthma is the most common chronic lower respiratory disease in childhood throughout the world. GINA (The Global Strategy for Asthma Management and Prevention) describes Asthma as a heterogeneous chronic airway disease very common in childhood, usually characterized by respiratory symptoms including wheeze, breathlessness, chest tightness and cough, together with variable expiratory airflow obstruction. Asthma most often starts early in life and has variable courses and unstable phenotypes which may progress or remit over time.

Epidemiology

Pediatric asthma is a serious public health problem around the world. The WHO (World Health Organization) estimated that approximately 300 million people currently have asthma worldwide, and with current trends rising, it is expected to reach 400 million by 2025. Nearly 250,000 people die prematurely each year from asthma, and most of all these deaths are preventable. The prevalence of current asthma is estimated at 6.7 % in adults and 8.5% in children, and the burden of asthma increased more than 75 % from 1999. Annually, the WHO has estimated that 15 million disability-adjusted life-years (DALYs) are lost. Globally, death rates from asthma in children range from 0 to 0.7 per 100,000 people. Approximately 500,000 annual hospitalizations (34.6% in individuals aged 18 y or younger) are due to asthma. Unfortunately, asthma is among the top 20 causes of DALYs for children of all ages and among the top 10 causes in the mid-childhood (ages 5–14 years). In the older age group (10–19 years), asthma has become more common cause of DAYLs over the last decade.

There is a large geographical variation in asthma prevalence, severity, and mortality. The prevalence is 8-10 times higher in developed countries (eg, United States, Great Britain, Australia, New Zealand) than in the developing countries. Most asthma-related mortality occurs in developing countries.

Race-, sex-, and age-related demographics

The prevalence of asthma is higher in minority groups (eg, blacks, Hispanics) than in other groups; nevertheless, increase in the prevalence is attributed to asthma in white children. Approximately 5–8 % of all black children have asthma at some time. The prevalence in Hispanic children is reported to be as high as 15 %. In blacks, the death rate is consistently higher than in whites.

Before puberty, the prevalence of asthma is 3 times higher in boys than in girls. During adolescence, the prevalence is equal among males and females. Adult-onset asthma is more common in women than in men.

In most children, asthma develops before age 5 years (50–80 %), and, in more than half, asthma develops before age 3 years.

Among infants, 20 % have wheezing with only upper respiratory tract infections (URTIs), and 60 % no longer have wheezing by age 6 years.

However, many of these children are "transient wheezers" whose symptoms subside during the preschool or early school years. They tend to have no allergies, although their lung function is often abnormal. These findings have led to the idea that they have small lungs.

Children in whom wheezing begins early in conjunction with allergies are more likely to have wheezing when they are aged 6-11 years. Similarly, children in whom wheezing begins after age 6 years often have allergies, and the wheezing is more likely to continue when they are aged 11 years.

Etiology

Asthma can begin at any age but most often has onset in early childhood. Asthma oridgin depends on both genetics and the environment, modifiable environmental factors. There are infections, exposure to microbes, stress, pollutants, allergens, and tobacco smoke as possible contributing factors. The development of allergen-specific IgE, especially if it occurs in early life, is an important risk factor for asthma, especially in developed countries. In most cases of asthma in children, multiple triggers or precipitants are recognized, and the patterns of reactivity may change with age. Treatment can also change the pattern.

Respiratory infections

Wheeze is common with respiratory syncytial virus (RSV) bronchiolitis and recurrent wheeze may persist up to 3–5 years. However, RSV is unlikely the sole explanation for the development of atopic asthma later in life. On the other hand, infection with human rhinovirus that requires hospitalization has been associated with future development of asthma (age 6 y). Most commonly, these are viral infections responsible for the development of wheezing. In some patients, fungi (eg, allergic bronchopulmonary aspergillosis), bacteria (eg, Mycoplasma, pertussis), or parasites may be responsible. From enormous quantity of natural fungi (about 100 000 kinds) allergic characteristics are detected in 300–350 kinds. The most widespread spore formative mold fungi, which predominate in atmosphere air (Cladosporium, Alternaria) and in the air of house (Aspergillum, Penicillium) are of greatest importance in Asthma etiology. Apart from it, other fungi (Mucor, Fusarium etc.), having more local circulation, can be the cause of sensibilization also. All of them discharge tremendous quantity of spores in the air, size of which are from 0,5 to 12 microns, due to it they invade respiratory ways with inspired air deeply. Most infants and young children who continue to have a persistent wheeze and asthma have high immunoglobulin E (IgE) production and eosinophilic immune responses (in the airways and in circulation) at the time of the first viral URTIs. They also have early IgE-mediated responses to topical aeroallergens.

Food allergens

Food allergens are the main sensibilization's factors for infants of first months of life, first of all there are cow's milk and formula on its base, afterwards – yolk and protein of the eggs, and semolina. So called asthma of

milk precipitates exists in small children, it combines often with inborn hyperreactivity of airways. Gradually sensibilization to food allergens diminishes. Increased sensitivity to inhalation, domestic and pollen allergens appears to 3–5 years. Monovalent allergy becomes polyvalent one.

Allergens and irritants

In patients with asthma, 2 types of bronchoconstrictor responses to allergens are recognized: early and late. Early asthmatic responses occur via IgE-induced mediator release from mast cells within minutes of exposure and last for 20–30 minutes. Late asthmatic responses occur 4–12 hours after antigen exposure and result in more severe symptoms that can last for hours and contribute to the duration and severity of the disease. Inflammatory cell infiltration and inflammatory mediators play a role in the late asthmatic response. Allergens can be foods, household inhalants (eg, animal allergens, molds, fungi, roach allergens, dust mites), or seasonal outdoor allergens (eg, mold spores, pollens, grass, trees).

Tobacco smoke, cold air, chemicals, perfumes, paint odors, hair sprays, air pollutants, and ozone can initiate bronchoconstrictor responses by inducing inflammation.

Other factors.

Asthma attacks can be related to changes in atmospheric temperature, barometric pressure, and the quality of air. In some children, emotional distress clearly makes asthma worse. Exercise can trigger an early asthmatic response. Heat and water loss from the airways can increase the osmolarity of the fluid lining the airways and result in mediator release. Cooling of the airways results in congestion and dilatation of bronchial vessels. During the rewarming phase after exercise, the changes are magnified because the ambient air breathed during recovery is warm rather than cool.

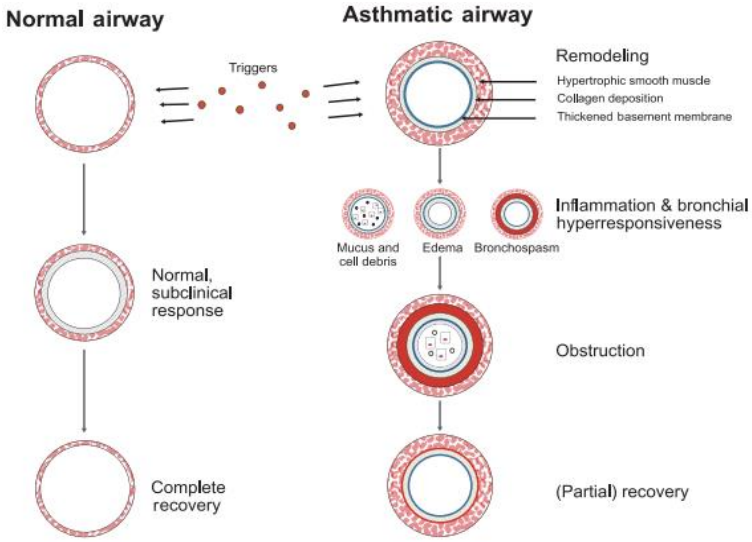
The presence of acid in the distal esophagus, mediated via vagal or other neural reflexes, can significantly increase airway resistance and airway reactivity. Inflammatory conditions of the upper airways (eg, allergic rhinitis, sinusitis, or chronic and persistent infections) must be treated before asthmatic symptoms can be completely controlled.

Multiple factors explain nocturnal asthma. Circadian variation in lung function and inflammatory mediator release in the circulation and airways (including parenchyma) have been demonstrated. Other factors, such as allergen exposure and posture-related irritation of airways (eg, gastroesophageal reflux, sinusitis), can also play a role. In some cases, abnormalities in CNS control of the respiratory drive may be present, particularly in patients with a defective hypoxic drive and obstructive sleep apnea.

Children exposed to higher maternal stress during the pre- and postnatal period have higher risk for asthma. This was only true in non-atopic mothers. Maternal obesity (BMI ≥ 35 and gestational weight gain $\geq$ 25 kg) during pregnancy increases risk of asthma and wheezing in the offspring.

Pathophysiology

Asthma is a disease of chronic inflammation, airway hyperresponsiveness (AHR), and chronic structural changes known as airway remodeling (*picture 1*).



Picture 1. In children, as in adults, pathological changes of the bronchi ('airway remodeling'), are present in the airways. Inflammation is triggered by a variety of factors, including allergens, viruses, exercise etc. These factors also induce hyperreactive responses in the asthmatic airways. Inflammation and hyperreactivity lead to airway obstruction. Although pathophysiological changes related to asthma are generally reversible, partial recovery is possible.

Persistent asthma is universally regarded as a disease of chronic airway inflammation. Increased populations of mast cells, eosinophils, lymphocytes, macrophages, dendritic cells, and others contribute to inflammation. Structural cells such as epithelial cells and smooth muscle cells may also contribute to the inflammatory environment. The inflammatory and structural cells collectively produce mediators such as cytokines, chemokines, and cysteinyl leukotrienes that intensify the inflammatory response and promote airway narrowing and hyperresponsiveness. AHR is associated with excessive smooth muscle contraction in response to nonspecific irritants and viral infections, and for allergic individuals, exposure to specific allergens. Neural mechanisms, likely initiated by inflammation, contribute to AHR.

Acute episodes of airway narrowing are initiated by a combination of edema, infiltration by inflammatory cells, mucus hypersecretion, smooth muscle contraction, and epithelial desquamation. These changes are largely reversible; however, with disease progression, airway narrowing may become

progressive and constant. Structural changes associated with airway remodeling include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion. Remodeling, initially described in detail in adult asthma, appears to be also present in at least the more severe part of the spectrum in pediatric asthma.

The current "hygiene hypothesis" of asthma illustrates how this cytokine imbalance may explain some of the sharp increases in asthma prevalence in developed countries. This hypothesis is based on the concept that the newborn's immune system deviates toward Th2 cytokine generation (mediators of allergic inflammation). Over time, environmental stimuli such as infections activate Th1 responses and bring the Th1/Th2 ratios to proper balance

Evidence suggests that the prevalence of asthma is reduced in children who experience the following events:

- Certain infections (Mycobacterium tuberculosis, measles, or hepatitis A)
- Rural living
- Impact of other children (eg, presence of older siblings and early enrollment in childcare)
- Less frequent use of antibiotics, including in the first week of life.
- Early introduction of fish in the diet.

The absence of these lifestyle events is associated with the persistence of a Th2 cytokine pattern.

Under these conditions, the genetic background of the child, with a cytokine imbalance toward Th2, sets the stage to promote the production of immunoglobulin E (IgE) antibody to key environmental antigens (eg, dust mites, cockroaches, Alternaria, and possibly cats). Therefore, a gene-by-environment interaction occurs in which the susceptible host is exposed to environmental factors that are capable of generating IgE, and sensitization occurs.

A retaliatory interaction is apparent between the two subpopulations, in which Th1 cytokines can inhibit Th2 generation and vice versa. Allergic inflammation may be the result of an excessive expression of Th2 cytokines. The loss of normal immune balance arises from a cytokine dysregulation in which Th1 activity in asthma is diminished.

Obesity is a determinant of asthma control independent of inflammation, lung function, and AHR.

Airway inflammation in asthma is mediated by a variety of cell subtypes, resulting in hyperresponsive airways, ultimately limiting airflow and causing variable symptoms. Initial airway bronchoconstriction is followed by airway edema and exaggerated mucus production, accompanied by AHR, and followed by chronic changes in the airway epithelium (airway remodeling). Current medical management targets various points along this continuum. However, no clear evidence suggests that early or aggressive treatment with anti-inflammatory medications, such as inhaled corticosteroids, can prevent airway remodeling.

Airway inflammation is mediated by a variety of cytokines and chemokines (cytokines that are specific for chemotaxis and activation of leukocytes). Cytokines are produced by a number of cell types, including lymphocytes, eosinophils, and mast cells. Proinflammatory cytokines (interleukin-4 [IL-4], IL-5, and IL-13), produced primarily by the T-helper (Th)2 lymphocytes, are believed to trigger the intense inflammation of allergic asthma. An imbalance between Th1 and Th2 lymphocytes (specifically, decreased Th1 activity with increased Th2 activity) contributes to chronic inflammatory asthma. Chemokines play a key role in inflammation. These proteins recruit proinflammatory cells, including Th2 lymphocytes, mast cells, neutrophils, and eosinophils. Eosinophils and mast cells have a distinct role in asthma pathogenesis. These cell types produce proinflammatory cytokines as well as leukotrienes, which cause bronchoconstriction.

The airway epithelium is a target for infectious, noxious, and environmental insults that cause injury via influx of proinflammatory cells and cytokines. Both viral infections and airborne allergens can precipitate a biphasic response that ultimately leads to asthma symptoms. IgE plays a main role in this process, as shown by evidence that administration of anti-IgE monoclonal antibodies reduces asthma symptoms and improves lung function. The IgE-mediated “early-phase” or “immediate” response to an allergen challenge causes mast cells and basophils to degranulate, precipitating bronchospasm as well as the release of proinflammatory cytokines and chemokines. This cascade of inflammatory responses results in the subsequent “late-phase” obstruction of air flow, which occurs 4 to 12 hours following exposure to the environmental insult. Bronchodilators can relax airway smooth muscle, if administered during the initial period of bronchospasm. However, due to the increased AHR and inflammation that occur with the late-phase response, bronchodilator therapy is not as effective, and anti-inflammatory medication is required.

The Asthma Predictive Index (API)

Recurrent wheezing is a common problem in young children. Approximately 40 % of all young children worldwide have at least 1 episode of asthmatic symptoms, such as wheezing, coughing, or dyspnea. Moreover, approximately 80 % of the asthmatic subjects have the disease in the first years of life. However, only 30 % of preschoolers with recurrent wheezing still have asthma at the age of 6 years.

Wheezing is very uncommon during the first two months of life, but in the next few months, first-time wheezing increases, peaking between two and five months of age. Infants' airways (compared to older children and adults) are smaller around, have less smooth muscle and make more mucus, which can lead to more coughing, wheezing, chest tightness, shortness of breath, or rapid breathing. Most wheezing during the first three years of life is related to viral respiratory infections, such as respiratory syncytial virus (RSV).

The 2007 National Heart, Lung and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma describes the API, a guide to deter**m**ining which small children will likely have asthma in later years.

Major criteria:

- Parental history of asthma
- Physician diagnosed eczema

Minor criteria:

- Physician diagnosed allergic rhinitis
- Wheezing not related to colds
- Blood eosinophilis (≥ 4 %)

A positive API score requires recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor criteria (physiciandiagnosis allergic rhinitis, wheezing without colds, or peripheral eosinophilia $\geq 4\%$).

A loose index (3 episodes/y and 1 of the major or 2 of the minor criteria) were created.

A positive stringent API score by the age of 3 years was associated with a 77 % chance of active asthma from ages 6 to 13 years; children with a negative API score at the age of 3 years had less than a 3 % chance of having active asthma during their school years.

Clinical aspects.

The clinical picture of pediatric asthma varies. Asthma exacerbation appears as a result of triggers action – ARI, allergens, physical and psychoemotional load, changes of meteorological situation, ecological impacts, intolerable products, vaccines and sera.

Attack of expiratory suffocation is typical. Attack appears more often at night or at 4–6 a.m. that is connected with circade rhythm of bronchial hyperreactivity. Patient's breathing becomes noisy, participation of abdominal press muscles, scalene muscles, sternocleidomastoid muscle in respiratory act is seen. Supra- and subclavicular spaces, intercostal intervals fall in. A patients feels fear; as a rule he tries to fix shoulder girdle, he sits leaning with his hands against knees; shoulders are raised and moved ahead, the head is pulled in shoulders, chest id elevated and enlarged at the expense of front-back size. Great majority of children has frequent anguished dry cough, increased BP and tachycardia.

Objectively at the moment of attack box-band shade of percussive pulmonary sound, low borders of lungs, narrowing of relative heart dullness borders, plenty of dry diffuse "musical" whistling wheezes at expiration and less of them at inspiration are revealed. In some patients not dry whistling wheezes but moist rales predominate, which can be auscultated both at expiration, and at inspiration. In such case we are speaking about so called "humid asthma". At the moment of attack temperature is normal, but short-term fever may be seen in infants without infectious process. Duration of attack may

vary from 30–40 minutes to several hours and even days (status asthmatic). Gradually facilitation takes place: patients begin to expectorate transparent foamy and than dense sputum, breathing becomes not so difficult, the face looks of normal color, but its edema may be preserved for a while. Epithelium cells, eosinofiles, macrophages and crystals of Sharko-Leiden may be revealed under microscope.

More 4 groups of symptoms are the diagnostic criteria of asthma:

- symptoms of respiratory discomfort: dry cough, predominantly in the early morning hours or after contact with allergen, its appearance and intensification after physical load, inspiration of strong smells, at meteorological changes;
- symptoms of reversible bronchial obstruction: expiratory dyspnea, box-band shade of pulmonary sound at percussion, dry whistling wheezes at expiration, and prolongation of expiration;
- extrapulmonary signs of allergy, burdened allergic anamnesis;
- eosiniphilia in blood and/or sputum.

Severity of asthma course is determined by degree of bronchial obstruction.

Wheezing.

A musical, high-pitched, whistling sound produced by airflow turbulence is one of the most common symptoms. The wheezing usually occurs during exhalation.

In the mildest form, wheezing is only end expiratory. As severity increases, the wheeze lasts throughout expiration. In a more severe asthmatic episode, wheezing is also present during inspiration. During the most severe episodes, wheezing may be absent because of the severe limitation of airflow associated with airway narrowing and respiratory muscle fatigue.

Asthma can occur without wheezing when obstruction involves predominantly the small airways. Thus, wheezing is not necessary for the diagnosis of asthma. Furthermore, wheezing can be associated with other causes of airway obstruction, such as cystic fibrosis and heart failure.

Coughing and chest tightness.

Cough may be the only symptom of asthma, especially in cases of exercise-induced or nocturnal asthma. Usually, the cough is nonproductive and nonparoxysmal. In addition, coughing may be present with wheezing. Children with nocturnal asthma tend to cough after midnight, during the early hours of morning. A history of tightness or pain in the chest may be present with or without other symptoms of asthma, especially in exercise-induced or nocturnal asthma.

Other nonspecific symptoms.

Infants or young children may have a history of recurrent bronchitis, bronchiolitis, or pneumonia; a persistent cough with colds; and/or recurrent croup or chest rattling. Most children with chronic or recurrent bronchitis have asthma. Asthma is the most common underlying diagnosis in children with recurrent pneumonia. Older children may have a history of chest tightness and/or recurrent chest congestion.

Criteria of asthma severity are determined on the base of attacks clinical characteristics, frequency of night attacks, tolerance to physical load, changes of FEV_1, PEF and daily bronchial lability (DBL), characteristics and duration of remission periods, mode of attack's arresting, duration and matter of base anti-inflammatory therapy (*table 1*).

Asthma exacerbation may proceed as acute attack or lingering condition of bronchial obstruction. Asthma attack is acute episode of expiratory dyspnea, difficult and/or whistling breathing and spastic cough at marked decrease of PEF that is exactly noted by patient and his associates.

Table 1

Criteria of asthma severity in children

	Intermittent asthma (I step)	*Persistence of asthma*		
		Mild degree of asthma (II step)	*Moderate degree of asthma (III step)*	*Severe degree of asthma (IV step)*
Frequency of attacks	Several times a year, not more frequent than once a month	3–4 times a month	More frequently than once a week but less frequently than once a day	Every day constantly
Clinical characteristics of attacks	Episodical, quickly disappearing, mild	Episodical, quickly disappearing, mild	Attacks of moderate severity with exact disorders of external respiration function	Constant presence of symptoms, severe attacks, asthmatic status
Night attacks, activity sleep disorders	Absent	Absent or present very rarely, the child episodically awakes	2–3 times a week, the child awakes	Almost every night, the child practically doesn't sleep
Tolerance to physical load	Not changed	Not changed	Decreased	Essentially decreased
Indices of FEV_1, PEF	Not less than 80 % of norm	Not less than 80 % of norm	60–80 % of norm	Less than 60 % of norm
Changes of bronchial patency during 24 hours	Not more than 20 %	Not more than 20 %	20–30 %	More than 30 %
Characteristics of remission periods	Normal values of external respiration function between exacerbations	Symptoms are absent, normal function of external respiration	Not complete clinical-functional remission	Not complete clinical-functional remission (respiratory insufficiency)
Characteristics of remission periods	Normal values of external respiration function between exacerbations	Symptoms are absent, normal function of external respiration	Not complete clinical-functional remission	Not complete clinical-functional remission (respiratory insufficiency)
Duration of remission periods	Short exacerbations (from several hours up to several days)	3 months and more	Less than 3 months	1–2 months
Physical development	Is not disturbed	Is not disturbed	Is not disturbed	Possibility of retardation and disproportion of physical development

Period of asthma exacerbation – lingering course of attack's period characterized with prolonged breathing difficulties, which can last days, weeks and months; clinically marked syndrome of bronchial obstruction is present. Acute asthma attacks of various severity can be seen in such condition (*table 2*).

Table 2

Criteria for evaluation of attack's severity

Signs	*Light*	*Mild*	*Severe*	*Threat of respiratory standstill (status asthmatics)*
Physical activity	Preserved	Limited	Forced position	Absent
Talking speech	Preserved	Limited: separate phrases are pronounced	Jerky speech	Absent
Conscience sphere	Excitement sometimes	Excitement	Excitement, fright	Mental confusion, hypoxic coma
Respiratory rate*	Hurried breathing	Expiratory dyspnea is present	Marked expiratory dyspnea	Tachypnea or bradypnea
Participation of auxiliary musculature, retraction of jugular fossa	Feebly marked	Marked	Strongly marked	Paradoxical thoracoabdominal breathing
Whistling breathing	Registered at the end of expiration as a rule	Marked	Strongly marked	"Mute lung", absence of respiratory murmurs
Pulse rate*	Increased	Increased	Markedly increased	Bradycardia
FEV1, PEF in % of norm or of best patient's indices*	More than 80 %	60–80 %	Less than 60 % of norm	
PaO2	Norm	More than 60 Hg mm	Less than 60 Hg mm	
PaCO2	Less than 45 HG mm	Less than 45 HG mm	More than 45 HG mm	

* Respiratory rate, pulse rate, FEV1, and PEF is necessary to repeat in dynamics of treatment.

The most severe form of asthma is distinguished in separate group – status asthmatics – that is connected obviously with peculiarities of clinical manifestations and medical tactics demanding immediate hospitalization of a patient to intensive care unit.

Non-arresting asthma attack with duration more than 6 hours or absence of positive dynamics after 3 adrenaline injections with intervals of 20–30 minutes are criteria of status asthmatics. Status asthmatics is caused by deep block of β_2-adrenoreceptors due to:

1. long term treatment of the disease with frequent exacerbations, that demanded wide use of sympathomimetics;
2. infectious processes in broncho-pulmonary system;
3. abrupt decrease of glucocorticoids in hormon-dependent patients.

Three stages of status asthmatics are distinguished:

I stage – stage of relative compensation. It is characterized by resistance to sympathomimetics and partially to other broncholitics. It appears more frequently not attack-like, but gradually and lasts for several days. Pallor of skin, acrocyanosis, expiratory dyspnea, swelling of chest, persistent cough and dry whistling wheezes on the background of weakened respiration ate typical. Discrepancy between intensity of respiratory wheezes, which can be heard at a distance and by direct lung's auscultation, attracts attention. Tachycardia, elevated BP, narrowing of heart's relative dullness borders due to lung's emphysema, are registered.

II stage of status asthmatics is characterized by increasing respiratory insufficiency of obstructive type: utmost severity of patient's condition, pale cyanosis, perioral and acrocyanosis, marked tachycardia, dyspnea, liver's enlargement, and edema. Practically total absence of wheezes at auscultation ("mute lungs") or very few dry wheezes on limited region seem to be paradoxical. Cough disappears, pulse is frequent and weak, BP is decreased. Formation of total bronchial obstruction syndrome is typical for this stage of status asthmatic that can lead to hypoxic coma if medical care is delayed. General excitement, sense of fear and asphyxia give place to prostration.

III stage of status asthmatics – hypoxemic coma and asphyctic syndrome develop due to decompensated respiratory and metabolic acidosis and marked hypercapnia. Chuchalin A.G. distinguishes 2 types of hypoxemic coma – quickly and slowly appearing ones. Prostration, early loss of reflexes and consciousness on the background of generalized cyanosis, increasing tachycardia and dyspnea, which loses expiratory component, decreasing BP, swelling of cervical veins, and liver's enlargement are typical for quickly proceeded hypoxemic coma. Wheezes are not auscultated any more, and so called "dead lungs" appear. The same symptoms are typical for slowly proceeded hypoxemic coma also, but its appearance is protracted in time.

Clinical sings in the absence of an acute episode.

The physical findings between acute episodes vary with the severity of the asthma. During an outpatient visit, a patient with mild asthma may have normal findings on physical examination. Patients with more severe asthma are likely to have signs of chronic respiratory distress and chronic hyperinflation.

Signs of atopy or allergic rhinitis, such as conjunctival congestion and inflammation, ocular shiners, a transverse crease on the nose due to constant rubbing associated with allergic rhinitis, and pale violaceous nasal mucosa due to allergic rhinitis, may be present.

The anteroposterior diameter of the chest may be increased because of hyperinflation. Hyperinflation may also cause an abdominal breathing pattern.

Lung examination may reveal prolongation of the expiratory phase, expiratory wheezing, coarse crackles, or unequal breath sounds. In a child who is not sick, forced exhalation may reveal expiratory wheeze.

Diagnostics of asthma.

Diagnostics of asthma is based first of all upon analysis of anamnesis and clinical manifestations with obligatory examination of FVD. It allows to evaluate degree of bronchial obstruction and its dynamics under the influence of treatment, and to determine more exactly both degree of attack's severity and degree of severity of asthma itself.

Total blood analysis is normal in uncomplicated asthma. Sometimes negligible eosinophilia is present. ESR is normal as a rule, its elevation testifies to addition of infection.

Sputum's examination. Macroscopically sputum is sticky, viscous and whitish. Cells of ciliary epithelium, neutrophils, a lot of eosinophils as well as elongated bipyramidal crystals (Sharko-Leiden) released from eosinophils are seen in sputum at exogenic asthma. Amount of eosinophils is less, neutrophils predominate if asthma is of endogenic origin.

Any changes on X-ray of the chest at interictal period of uncomplicated Asthma are absent. Increased transparence of lung's fields and flattening of diaphragm's cupola appear during attack. Segmental and subsegmental atelectasis may appear due to bronchial obstruction with mucous corks.

Total level of IgE in blood's plasma is usually elevated in exogenic asthma.

Pulmonary Function Tests/Spirometry is recommended in children older than 5 years for routine management of asthma and when the diagnosis is in question. Spirometry is more accurate than PEF. The 2 readings important in the diagnosis and evaluation of Asthma are forced expiratory volume in1 second (FEV1) and the ratio of FEV1 to forced vital capacity or FEV1%. FEV1% is the proportion of forced vital capacity a child is able to expire in 1 second. The goal of PFT in asthma is to document expiratory flow limitation or obstruction with reversibility. An FEV1% of less than 80% is diagnostic for airflow obstruction, and reversibility with administration of a bronchodilator is diagnostic for asthma. FEF 25-75 is a sensitive indicator of obstruction and may be the only abnormality in a child with mild disease. If a child is able to fully cooperate, an FEV1% greater than 80% is normal. The classic flow-volume curve for asthma shows a dampening and scooping out of the expiratory curve.

One of the main points in asthma diagnostics at early stages of disease is the exposure of non-specific bronchial hyperreactivity. Test with physical load is one of the most available one for it. PEF before load is measured, than physical load is given during 6-8 minutes. Immediately after loading and in 5-10 minutes PEF is measured. If PEF decreases more than 12% of initial meaning – test is considered to be positive. Provocative inhalation tests with non-specific agents (histamine, metacholine), cold air, and ultrasound spray with distilled water are used also. Provocative tests are used in a period of Asthma remission.

An index of bronchial obstruction's reversibility is important diagnostic and prognostic criterion. FEV1 is measured, afterwards the patient inhales one dose of b2-agonist, and indices of spirometry are repeatedly registered in 15 minutes. Increasing in FEV1 >12% suggests a significant bronchodilation and obstruction's reversibility. negative (10%).

In an outpatient or office setting, measurement of the peak flow rate by using a peak flow meter can provide useful information about obstruction in the large airways. Peakflowmetry allows measuring peak expiratory flow (PEF) 2-3 times a day at home. Patients with asthma use the changes in PEF readings to help reveal how their lungs are functioning, and how well they are responding to treatment.

Allergologic investigation is made in vivo or in vitro depending upon child's age, period of illness, and presence of attendant pathology for confirmation of prospective spectrum of sensibilization. Scarificative skin allergic tests are made during a period of remission, allergic specific IgE are measured during exacerbation period.

Determination of nitrogen oxide's (NO) concentration in expired air is one of the modern non-invasive methods for diagnostics of allergic inflammation in Asthma. Very shortly living (during several seconds) molecules of this gas are synthesized by vessel's endothelium, macrophages, neutrophils, mast cells, platelets, and epithelium cells of bronchial mucous membrane. Their concentration increases trustworthy in Asthma and decreases on the backckground of treatment with inhale corticosteroids. NO concentration in expired air is decreased in chronic obstructive disease of adults and mucoviscidosis.

Differential diagnosis.

Differential diagnosis of Asthma is made with conditions for which bronchoobstructive syndrome is typical.

Obstructive bronchitis, acute bronchiolitis: clinical features of acute respiratory infection, intoxication, absence of atopy are typical.

Foreign bodies of respiratory ways: patients mark precise time of condition's worsening, which is manifested as acute asphyxia with or without cyanosis and following cough. X-ray of the chest and bronchoscopy are necessary.

Stenosing laryngotracheitis – clinical symptoms appear more frequently in the evening or at night on the background of catarrhal manifestations, fever, hoarse voice, inspiratory dyspnea, and typical barking cough.

Cardiac Asthma – is seen in patients with inborn heart disease; enlargement of cardiac borders, muffled tones, cardiac murmurs, peripheral edema, liver's enlargement, bubbling respiration, moist rale[s], and predominantly inspiratory dyspnea are typical.

Mucoviscidosis – retardation of physical development, absence of atopy, external respiration's disorders of mixed type, recurrent pneumonia, diarrhea

with steatorrhea, and increased content of sodium and chlorides in sweat are present.

Exogenic allergic alveolitis – a disease provoked by inspiration of organic dust with various allergens which is characterized with diffuse affection of alveolar and interstitial lung's tissue. Disorders of common condition, respiratory insufficiency, expiratory dyspnea, specific fine bubbling "cellophane" rales are typical. At X-ray symptom of "focusing screen" and disorders of external respiratory function are seen.

Treatment of Asthma.

Modern treatment of bronchial asthma in children is pathogenetic and issues of key statement that Asthma – it is chronic disease, in which bronchial mucous membrane's inflammation constitutes its pathogenetic base. It is degree of inflammation's expression that determines severity of symptoms, character of course, prognosis and development of complications.

The main therapy's tasks are:

- struggle with chronic inflammatory process in respiratory ways;
- decrease of bronchial sensitivity;
- liquidation or relief of disease's clinical manifestations, diminishing of frequency and severity of exacerbations, normalization or improvement of indices of external respiration function;
- prevention of exacerbations and complications, disability and morbidity;
- prevention of side effects of drug therapy;
- reduce the need for a short-acting beta2-agonist (SABA) for quick relief of symptoms (not including prevention of exercise-induced bronchospasm)
- improvement of life's quality.

Disease control and improvement of life's quality in modern conditions are achieved due to following abilities:

1.trigger factors elimination;

2.pharmacotherapy;

3.specific hyposensibilization.

Revelation and maximally possible elimination of trigger factors have considerable mean in Asthma treatment. In cases when organism's contact with causative allergen is successfully interrupted or at least allergen's influence is decreased it's possible to prevent attack, decrease quantity of exacerbations, diminish intensity of drug therapy and stop growth of Asthma severity.

The asthma management strategy should include a periodical assessment of asthma control combined with adjustments (if needed) of treatment based on the level of control. It is strongly recommended to use asthma treatment in a stepwise approach with the ultimate goal of achieving "optimal" control with "minimal" amount of medications and dosage. Adherence to the prescribed

medications and the proper use of their devices are recommended to be addressed before any modification of the treatment plan. It is extremely important to select the best device for optimal treatment delivery (*tabl. 3*).

Table 3

Choosing an inhaler device for children 5 years and younger adolescents according to the GINA guideline 2019

Age (years)	Preferred device	Alternative Device
0–3	Pressure MDI + dedicated spacer with face mask	Nebulizer with face mask
4–5	Pressure MDI + dedicated spacer with mouthpiece	Pressure MDI + dedicated spacer with face mask or nebulizer with mouthpiece or face mask

Adapted from the GINA 2019. MDI = Metered –dose inhaler

Nebulizer, the only viable alternative delivery systems in children, are reserved for the minority of children who cannot be use of a spacer device. If nebulizer is used for delivery of ICS, it should be with a mouthpiece to avoid the medication reduce static charge.

Worldwide, different guidelines for the management of asthma in childhood are in use. Many countries have a unique guideline. The GINA guideline and the British Guideline on the Management of Asthma are leading and available for many physicians around the world. Table 4 shows a working schema for assessing asthma control in children 5 years and younger as suggested in the GINA guidelines.

Table 4

GINA Assessment of asthma control in children 5 years and younger adolescents according to the GINA guideline 2019

Symptom control		Level of asthma symptom control		
In the past 4 weeks, has the child had:		Well controlled	Partly controlled	Uncontrolled
Daytime asthma symptom for more than a few minutes,more than once a week?	Yes [] No[]	None of these	1–2 of these	3–4 of these
Any activity limitation due asthma? (runs/play less than other children, tires easily during walks/playing?)	Yes [] No[]			
Reliever medication needed more than once a week?	Yes [] No[]			
Any night waking or night coughing due to asthma?	Yes [] No[]			

Asthma pharmacotherapy includes use of medicaments in order to influence upon inflammatory changes of bronchial mucous membrane and obstruction mechanisms, which are connected with them:

1. Quick-Relief Medications

These drugs, including short-acting inhaled or oral beta$_2$ agonists, short-course oral corticosteroids, are taken as needed for immediate relief of acute symptoms and before exercise to prevent exercise-induced bronchospasm.

Short-acting beta$_2$ agonists (SABA) rapidly relax bronchial smooth muscle and are the therapy of choice to relieve acute symptoms and prevent exercise-induced bronchospasm. Beta$_2$ agonists relieve symptoms but do not affect the underlying disease. These agents have a good safety record but are subject to overuse because they provide rapid relief and have a short duration of effect. Overuse reduces their efficacy and has been associated with increased bronchial hyper-reactivity, central nervous system overstimulation, worsening asthma and death.

Oral corticosteroids have broad anti-inflammatory effects and may be used in a limited, short course (three to 10 days) to gain initial control of the asthma and speed resolution of moderate-persistent or severe-persistent exacerbations.

2. Long-term control medications

Controller medications include the following:

- Inhaled steroids (ICS)
- Combination products that contain ICS and long-acting beta$_2$-agonists (LABA). They include the combinations fluticasone-salmeterol (Advair, Seretide), budesonide-formoterol (Symbicort), fluticasone-vilanterol (Breo, Ellipta) and mometasone-formoterol (Dulera).
- Theophylline
- Leukotriene receptor antagonists (LTRA)
- Omalizumab injection

Medications for long-term control should be taken daily to maintain control of asthma and prevent exacerbations. Inhaled corticosteroids are the most potent and effective long-term anti-inflammatory medications. They reduce inflammation in airways, improve pulmonary function to a greater degree than any other medication, reduce bronchial hyperresponsiveness and may reduce some aspects of airway remodeling, thus modifying disease progression. Some corticosteroids are effective in once- or twice-daily dosing regimens and may be used in all patient groups and for all levels of disease severity. Doses of anti-inflammatory drugs for asthma treatment are shown in the *table 5, 6*.

Table 5

Low, medium and high daily doses of ICS for children and adolescents adolescents according to the GINA guideline 2019

Drug	Low daily dose (mcg)	Medium daily dose (mcg)	High daily dose (mcg)
Children 5 years and younger			
Beclomethasone dipropionate (HFA) Budesonide nebulized Fluticasone propionate (HFA) Mometasone fuorate	100 (≥ 5y) 500 (≥ 1y) 50 (≥ 4y) 110 (≥ 4y)		

Drug	Low daily dose (mcg)	Medium daily dose (mcg)	High daily dose (mcg)
Children 6–11 years			
Beclomethasone dipropionate (CFC)	200–500	> 500–1000	> 1000
Beclomethasone dipropionate (HFA)	100–200	> 200–400	> 400
Budesonide (DPI)	200–400	> 400–800	> 800
Ciclesonide (HFA)	80–160	> 160–320	> 320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI)	100–250	> 250–500	> 500
Fluticasone propionate (HFA)	100–250	> 250–500	> 500
Mometasone fuorate	110–220	> 220–440	> 440
Triamconolone acetonide	400–1000	> 1000–2000	> 2000

Table 6

Low, medium and high daily doses of ICS for children and adolescents adolescents according to the GINA guideline 2019

Drug	Low daily dose (mcg)	Medium daily dose (mcg)	High daily dose (mcg)
Adults and adolescent (12 years and older)			
Beclomethasone dipropionate (CFC)	100–200	> 200–400	> 400
Beclomethasone dipropionate (HFA)	50–100	> 100–200	> 200
Budesonide (DPI)	100–200	> 200–400	> 400
Budesonide nebulized	250–500	> 500–1000	> 1000
Ciclesonide (HFA)	80	> 80–160	> 160
Fluticasone furoate (DPI)	n.a.	n.a.	n.a.
Fluticasone propionate (DPI)	100–200	> 200–400	> 400
Fluticasone propionate (HFA)	100–200	> 200–500	> 500
Mometasone fuorate	110	≥220–440	≥ 440
Triamconolone acetonide	400–800	> 800–1200	> 1200

HFA hydrofluoroalkane propellant; CFC – chlorofluorocarbon propellant; DPI – dry powder inhaler; n.a. – not aplplicable

Theophylline produces mild-to-moderate bronchodilation and may be used as add-on therapy with anti-inflammatory medications. However, theophylline has a narrow therapeutic index, variable clearance rates, drug interactions and serious side effects; therefore, monitoring of blood levels is required. Theophylline is reserved for the treatment of patients with severe asthma, when polypharmacy is necessary.

Leukotriene receptor antagonists montelukast (Singulair) and zafirlukast (Accolate) are unique in their ability to target specific components of asthmatic inflammation. They reduce bronchospasm, decreased vascular permeability, mucosal edema, and inflammatory cell infiltration.

A stepwise approach for pharmacotherapy management in asthmatic patients has been proposed (*table 7*). Treatment starts at the step most appropriate to the initial severity of asthma. If control is not achieved within 3 months, stepping-up should be tried, after reconsidering adherence to therapy, environment factors, and associated co-morbidities; otherwise, treatment step down may be attempted once good asthma control and the patient's lowest effective level of treatment has been found and maintained for about 3 months. Each recommendation has been assessed for adults adolescents (over 12 years)

and children (5–12 years, and under 5 years) in all guidelines. Controller recommendations are divided into "preferred" and "other".

Table 7

Personalized management of asthma for children and adolescents according to the GINA guideline 2019

Age	Step 1	Step 2	Step 3	Step 4	Step 5
< 5 y	As-needed inhaled SABA	Regular daily low-doses ICS	Moderate dose ICS (double the low daily dose)	Continue controller & refer for specialist assessment	
		Other controller options: LTRA or intermittent ICS	*Other controller options*: Low dose ICS+LTRA Consider specialist referral	*Other controller options*: Add LTRA or increase ICS frequency, or add intermittent ICS	
	As-needed SABA				
6-11 y		Daily low dose ICS	Low-dose ICS-LABA or medium dose ICS	Medium-dose ICS – LABA Refer for expert advice	Refer for specialist assessment ±add-on therapy, e.g. anti-IgE
	Other controller options: low dose ICS taken whenever SABA taken, or daily low dose ICS (separate ICS and SABA)	*Other controller options*: LTRA, or low dose ICS taken whenever SABA taken	*Other controller options*: low dose ICS+LTRA	*Other controller options*: high-dose ICS-LABA, or tiotropium, or add-on LTRA	*Other controller options*: Add-on anti-Il5, or add-on low dose OCS, but consider side effects
	As-needed SABA				
12 y or older	As-needed low dose ICS-formoterol	Daily low-dose ICS, or as-needed low dose ICS-formoterol	Low-dose ICS - LABA	Medium-dose ICS - LABA	High-dose ICS - LABA Refer for specialist assessment ±add-on therapy, e.g. tiotropium, anti-IgE, anti-Il5/5R, anti-Il4R
	Other controller options: low dose ICS taken whenever SABA taken	*Other controller options*: LTRA, or low dose ICS taken whenever SABA taken	*Other controller options*: medium dose ICS , or low dose ICS+LTRA	*Other controller options*: high-dose ICS, add-on tiotropium, or add-on LTRA	*Other controller options*: add-on low dose OCS, but consider side effects
	As-needed low dose ICS-formoterol		As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy		
	As-needed SABA				

Treatment of asthma exacerbation in child

Asthma exacerbations, should be treated promptly and efficiently, otherwise it may result in rapidly culminate in life-threatening situations. Assessment of the severity of exacerbation of asthma is presented in table 2.

Children with symptoms of mild exacerbation can receive treatment at home. The parent or care should initiate treatment with puffs of inhaled SABA (200mcg by pMD + spacer or 2.5 mg by nebulizer for children under 5 years, 4-10 puffs by pMD + spacer for children 6–11 years) every 20 min for 1 hour and prednisolone 1–2 mg/kg orally. Parents should evaluate the condition of the child every 1 hour. If the condition worsens, the child should be transferred to the acute care facility.

Children with features of a severe exacerbation that fail to resolve within 1–2 hours despite repeated dosing with inhaled SABA, with or without OCS, must be referred to hospital for observation and further treatment.

Emergency treatment includes:

- Treatment hypoxemia urgently with oxygen by face mask to achieve and maintain percutaneous oxygen saturation 94–98 %.
- Bronchodilator therapy. The initial dose of SABA may be given by a pMD with spacer and mask or mouthpiece or an air-driven nebulizer; or, if oxygen saturation is low, by oxygen-driven nebulizer.
- Systemic corticosteroids. Rout of delivery: oral administration it as effective as intravenous. Dosage: OCS dose of 1–2 mg/kg up to a maximum of 40 mg/day is adequate. Duration: 3- and 5-day course is usually considered sufficient.
- Inhaled corticosteroids. High-dose ICS given within the first hour after presentation reduce the need for hospitalization in patients not receiving systemic corticosteroids
- Other treatments:

- Ipratropium bromide (2 puffs of ipratropium bromide 80 mcg or 250 mcg by nebulizer every 20 minutes for 1 hour only)
- Magnesium sulfate (nebulized isotonic magnesium sulfate (150 mg) 3 doses in first hour for children aged ≥ 2 years with severe exacerbation
- Leukotriene receptor antagonists.

Control questions

1. Mild episodic atopic asthma was diagnosed in a child of 7 years old. What drugs must be used for basic treatment in this case?

A. Euphyllin. *C. Dimedrol*. *E. Salbutamol*.
B. Budesonid. *D. Intal*.

2. A boy of 3 years old suffers from persistent asthma of mild degree. Which drug is the most rational for treatment of attack in this case?

A. Intal. *C. Becotid*. *E. Budesonid*.
B. Salbutamol. *D. Dimedrol*.

3. A boy of 11 years for last 4 years suffers from asthma with exacerbations during ambrosia and poplar blossoming. He suffers from ARI not more frequent than twice a year. What is the dominant pathogenetic mechanism of disease's development in this case?

A. Autoimmune. *C. IgE – regain.* *E. Immunocomplex.*
B. Microbial-inflammatory. *D. Neurogenic.*

4. Inhalation glucocorticosteroids were prescribed as basic anti-inflammatory therapy for 10-years-old boy suffering from moderate asthma. Indicate mostly useful drug from the group of glucocorticosteroids.

A. Budesonid. *B. Simbicort.* *C. Salmeterol.* *D. Mametason.*

5. Which of mentioned drugs are used for treatment of moderate asthma?

A. Indometacin, voltaren. *C. Fluticasone.* *E. Epinephrine.*
B. Intal, tailed. *D. Prednisolon.*

6. A girl of 9 years has asthmatic fits 3–4 times a month, which are treated with salbutamol. She is under supervision of a doctor since 5 years old. Indices of external respiration are the following: lung vital capacity – 91 %, forced expiratory volume, $(FEV)_1$ – 74 %, PEF – 69 %; daily bronchial lability – 20 %. What is degree of severity of bronchial asthma in this child?

A. Severe. *C. Mild.* *E. Status asthmaticus.*
B. Moderate. *D. Period of remission.*

7. A boy of 10 years complains of attack-like dry cough early in the morning. Objectively: expiratory dyspnea, forced position in a bed. At percussion – band box sound, at auscultation – dry whistling rales. In blood test: eosinophilia. What disease can be suspected?

A. Acute obstructive bronchitis. *D. Foreign body in bronchus.*
B. Bronchial asthma. *E. Pneumonia.*
C. Recurrent bronchitis.

8. A child suffers from bronchial asthma during 4 years. Asthmatic fit developed on the background of acute respiratory infection. What drugs are necessary to prescribe for treatment of attack?

A. Antibiotics. *C. Mucolytics.* *E. Corticosteroids.*
Б. β-2 agonists. *D. Antihistaminic.*

9. Attacks of dyspnea, cough (at first dry, afterwards productive) occur periodically (spring, autumn) in a girl of 14 years old. Objectively: chest is inflated, distended in anteroposterior part, RR – 32/min. At auscultation – dry whistling rales and prolonged expiration. Blood test – Hb-120 g/l, WBC – 8×10^9/l, stab neutrophils – 1 %, segmented neutrophils – 52 %, eosinophils – 8 %, lymphocytes – 36 %, monocytes – 3 %, ESR – 7mm/h. What is probable diagnosis?

A. Acute respiratory disease. *D. Bronchial asthma.*
B. Pneumonia. *E. Obstructive bronchitis.*
C. Cystic fibrosis.

10. During 8 hours asthmatic fit which can't be treated with adrenomimetics is seen in a boy of 11 years who suffers from bronchial asthma since 3 years old. Objectively: acrocyanosis, expiratory dyspnea, distant rales, at percussion – band box sound, at auscultation – dry whistling rales at expiration, tachycardia. There is discrepancy between respiratory noises heard at distance and rales heard directly at auscultation. What is the most probable diagnosis?

A. Period of attack of bronchial asthma.
B. Moderate bronchial asthma.
C. Status asthmaticus of I degree.
D. Status asthmaticus of II degree.
E. Status asthmaticus of III degree.

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