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Principles of Diagnosis and Therapy of Bronchial Asthma in Children at the Present Stage: GINA 2014-2015 Review Updates

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Bronchial asthma is one of the most prevalent respiratory diseases. There is a wide range of efficient drugs characterized by high safety profile and acceptable price for patients with this disease. However, a large number of patients receives inadequate treatment, which results in reduced quality of life, development of persistent bronchial obstruction and even death. In 2014, the Global Initiative for Asthma (GINA) significantly updated their regular issue "Global Strategy for Asthma Management and Prevention". It includes the current information on asthma and recommendations for clinical practice. This article presents the updates published in that document in 2014 and 2015. The authors present contemporary approaches to diagnosis, including differential diagnosis, of bronchial asthma in children, as well as up-to-date objectives and principles of therapy of this disease. The article covers assessment criteria of disease control and asthma severity in pediatric patients and presents analysis of possible problems of achieving adequate disease control.

Keywords: children, bronchial asthma, Global Strategy for Asthma Management and Prevention, diagnosis, treatment, control levels.

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RELEVANCE

Bronchial asthma (BA) is one of the most prevalent respiratory diseases. According to the World Health Organization (WHO), ca. 235 million people around the world suffer from asthma. Bronchial asthma is one of the most common non-infectious diseases among children.

The issue of asthma is relevant both for economically developed countries and countries with low standard of living. Despite the progress achieved in development of a strategy of diagnosis and therapy of this disease, this pathology is diagnosable and treatable not sufficiently well. Bronchial asthma is the main cause of 180,000 deaths per year. Most fatal outcomes caused by this disease are observed in countries with average and low standard of living.

MAIN GINA APPROACHES TO DIAGNOSIS AND THERAPY OF BA

The Global Initiative for Asthma (GINA) has been functioning under the aegis of the WHO and with support of the US National Heart, Lung and Blood Institute since 1992. The task force's goal is to reduce rates of mortality and disability caused by this disease by developing and introducing into practice an optimal strategy of managing patients with bronchial asthma and preventing thereof. The task force has been developing and keeping report "Global Strategy for Asthma Management and Prevention" up to date since then [2].

The Initiative's web-site contains freely accessibly up-to-date information for physicians, nurses, patients and their representatives on causes and mechanisms of the disease, risk factors and rational methods of asthma diagnosis and treatment. Apart from the main report, the web-site contains brief pocket guidelines for medical personnel in the primary healthcare, slides for teaching physicians treatment and prevention of asthma in adults and over-6 children, as well as in under-5 children. The attention is attracted primarily to the inhalation technique: the web-site contains freely accessible instructions for use of inhalation devices and a review of various modifications of spacers. Popularity and impact of the asthma task force reports have achieved such a high level that from 2015 the GINA does not require external financial support and is self-sustainable.

Recent radical changes to document "Global Strategy for Asthma Management and Prevention" were introduced in 2014 [3]. Such a serious review was required primarily due to discouraging data indicating that control of this disease remains insufficient, as well as observance of recommendations of guidelines on diagnosis and management of patients with this disorder, in many countries despite accessible modern means of asthma management. That is why the authors were to design a document that would promote a large-scale implementation of effective diagnostic and treatment methods. The renewed report contains presuppositions based on the evidence-based medicine principles, oriented at needs of the real clinical practice and presented in a convenient form.

Clinical manifestations of BA

According to GINA-2014, asthma is a heterogenous disease usually characterized by a chronic inflammation of airways. Typical anamnestic observations at asthma include such respiratory symptoms as sibilant rales, out-of-air feeling (dyspnea, asphyxia), chest congestion and cough. Symptoms may vary with time; they may also vary in severity (different degrees of restriction of the expiratory respiratory flow).

It is known that restriction of exhalation at asthma is caused by bronchoconstriction, bronchial wall thickening and increased mucus production in the airway lumen. Asthma symptoms may be provoked by various factors, including virus infections, allergens, tobacco smoke (active and passive smoking), physical exercises and stresses [2, 4, 5].

Diagnosis

Despite wide spread of bronchial asthma in the population, it may be rather difficult to diagnose, especially in infants. There is no single test that would allow diagnosing this disease with 100% confidence. Such a diagnosis is established taking into account a combination of the following data:

- characteristic symptoms in the anamnesis;
- bronchial obstruction reversibility confirmed by a bronchial spasmolytic-involving test or other tests;
- information on asthma symptoms in the patient's medical documents [3].

Although asthma is characterized by airway inflammation and bronchial hyperreactivity, the tests confirming presence of these symptoms are neither obligatory nor significant for diagnosis establishment [3]. Aggravation of the aforementioned symptoms at night or in the early morning, as well as their connection with virus infections, allergen action, physical stress, weather changes, laughing, inhalational effect of tobacco smoke, exhaust fumes and acrid odors indicate asthma. Such symptoms as isolated cough without other respiratory manifestations, inspiratory dyspnea with stridor after physical stress, chest pain, respiratory distress accompanied by vertigo, which may vary in the degree of manifestation, or peripheral paresthesias and chronic expectoration challenge diagnosis “Bronchial asthma” [3]. Many patients are also characterized by signs of atopic disease; however, positive results of skin tests and/or high level of specific immunoglobulin E do not always indicate this disease, as these symptoms are typical of several other nosological forms as well (allergic rhinitis, atopic dermatitis etc.). It should be noted that negative results of allergological examination do not allow ruling asthma out in case of non-atopic phenotype of this pathology [2, 4, 5].

Given considerable difficulty of analyzing respiratory function in children under 5-6 years of age and pronounced heterogeneity of causes of sibilant rales in this age group, it is necessary to extremely carefully analyze anamnesis and physical data for diagnostic purposes. It is necessary to note recurrent expiratory sibilant rales and/or non-productive cough (up to emesis) with or without dyspnea provoked or aggravated by trigger factors (allergens, physical exercises, laughing, shouting/crying, tobacco smoke, air pollutants) or at night and not related to a respiratory infection.

However, it is well-known that asthma symptoms in infants and preschoolers may often manifest themselves in the setting of a respiratory infection. In such cases it is rather difficult to distinguish asthma from temporary sibilant rales occurring in the setting of acute respiratory infections.

Evaluation of physical exercise tolerance should be given specific attention as parents do not usually associate respiratory symptoms with their child's active movements, or the child limits his/her physical activity himself/herself. If a child cannot run, play and laugh as well as his/her age-peers and gets tired quickly when walking (asks to be carried on hands) due to dyspnea or paroxysmal cough, consider the possibility of asthma.

Bronchial asthma in the closest relatives, as well as other allergic diseases in familial anamnesis (such as atopic dermatitis or allergic rhinitis) also allow suspecting asthma as the cause of recurrent sibilant rales, non-productive cough and dyspnea.

Sometimes it is difficult to definitely prove or rule out asthma in a child on the basis of the aforementioned data. In such cases it is reasonable to conduct trial treatment with low-dose inhalation corticosteroids (IHCS) and short-acting β_2 -agonists (SABA) as required for 2-3 months and obligatory subsequent evaluation of therapeutic effect [3]. Significant clinical improvement is observed in patients with bronchial asthma; if the condition does not improve or aggravates, it is necessary to discontinue therapy and consider the chance of a different disease (table 1). Congenital and hereditary respiratory diseases accompanied by bronchial obstructive syndrome are often diagnosed late, and patients are followed up as suffering from bronchial asthma on a long term [9, 10].

GINA-2014 features a revised approach to the evaluation of hissing respiration episodes in under-5 children proposed by this consensus previously: they are classified on the basis of the nature of occurrence (periodic [in the setting of acute respiratory infections] and multifactorial [caused by any other reason]) or age (transitory [occurring before 3 years of age], early-onset [occurring at the age of 3-6 years] and late-onset [symptoms occur after 3 years of age]). These classifications have recently been declared useless for real clinical practice [3], although it should be noted that they were never traditionally used in Russia.

Table 1. Differential diagnosis of asthma in children [2, 6, 7 with amendments]

Pathology	Typical manifestations
Recurrent respiratory viral infections	Primarily cough, nasal discharge and nasal congestion for < 10 days; usually mild hissing respiration; no symptoms without infection episodes
Gastroesophageal reflux	Recurrent bronchitis, cough, insufficient effect of antiasthmatic therapy. Over-excitability, emesis, heartburn (especially after intake of a large amount of food) may occur
Foreign body aspiration	Rough severe cough episode and/or stridor during eating or playing in the anamnesis; recurrent bronchitis, protracted pneumonia and cough, local changes in the lung (atelectasis, unilateral emphysema). Rales are usually unilateral
Tracheoesophageal fistula, dysphagia	Recurrent bronchitis, protracted pneumonia and cough, choking during eating or drinking, occurrence or aggravation of pulmonary rales after eating or drinking
Tracheomalacia or bronchomalacia	Noisy respiration during crying, eating or in the setting of acute respiratory infection, rough cough, inspiratory or expiratory chest retraction; symptoms are usually observed as early as immediately after birth; insufficient antiasthmatic therapy effectiveness
Tuberculosis	Continuous noisy respiration and cough; fever refractory to standard antibiotics; enlargement of lymph nodes; insufficient response to bronchodilator or IHCS therapy; contact with a tuberculosis patient
Congenital heart defects	Cardiac murmur, cyanosis while eating, poor weight gain, tachycardia, tachypnea or hepatomegaly, insufficient antiasthmatic therapy effectiveness
Mucoviscidosis (cystic fibrosis)	Cough develops almost immediately after birth, recurrent respiratory infections, poor weight gain due to malabsorption, abundant liquid fatty stool
Primary ciliary dyskinesia	Cough and (usually) mild or moderate recurrent respiratory infections; chronic otitis, purulent nasal discharge; insufficient antiasthmatic therapy effectiveness; <i>situs inversus</i> in ca. 50% of the children
Vascular ring	Frequent continuous noisy respiration, rough metallic cough, dysphagia at swallowing solid food, insufficient antiasthmatic therapy effectiveness
Bronchopulmonary dysplasia	In most cases occurs in premature infants; very low birth weight, need in long-term artificial pulmonary ventilation or oxygen therapy; respiratory disorders present from birth
Primary immunodeficiency conditions	Recurrent fevers and infections (including non-respiratory infections); poor weight gain
Psychogenic cough	Loud cough not related to allergens, respiratory infection or physical exercises; possible connection with negative psychoemotional factors; no symptoms during sleep
Affective-respiratory paroxysms	Complaints of difficulty inhaling; episodes often start with frequent full inspirations; improvement at breath-holding

Treatment

It is universally accepted that asthma is a chronic disease not treatable in contemporary conditions; however, there are effective and minimally risky means of ensuring high quality of life for patients. That is why the main goal of bronchial asthma therapy is to achieve control over the disease, which consists in observation of symptoms and regulation of risk factors of adverse outcomes, provision of high level of physical activity, minimization of risks of exacerbations and treatment-related side effects, as well as prevention of fixed bronchial obstruction development [3].

According to the updated GINA consensus document, asthma treatment should consist in a cyclical continuous process involving evaluation of a patient's condition, correction of drug or drug-free therapy and compulsory control of response to the conducted treatment. Asthma control assessment is based on the disease symptoms registered in 4 previous weeks (tables 2, 3).

Risk factors of exacerbations

Along with assessing BA symptoms it is necessary to consider possible risk factors of exacerbations and, accordingly, of adverse outcomes. If a patient has at least one of them, the risk of exacerbation development increases even if bronchial asthma symptoms may be considered well-controlled. Risk factors should be assessed in the beginning of the therapy and later, 3-6 months after launching baseline therapy.

Such factors include [3]:

- severe exacerbation of asthma, which required intubation and artificial pulmonary ventilation, in the anamnesis;
- hospitalization or recourse to emergency care within the previous year;
- use or recent withdrawal of systemic corticosteroids;
- absence of baseline IHCS therapy or failure to comply with the prescribed IHCS regimen or misuse of an inhaler;
- psychiatric illnesses in the anamnesis or psychosocial issues;
- low adherence to baseline BA therapy and/or low compliance to written medical recommendations on BA therapy (or absence of written recommendations);
- food allergy realized in a patient as symptoms of bronchial asthma (may indicate that asthma in this patient is one of the manifestations of anaphylaxis);
- eosinophilia in sputum or clinical blood assay;
- pregnancy;
- excessive use of SABA (according to GINA-2015, use of more than 1 200-dose can of salbutamol or other drug in the equivalent dosage per month leads to risk of death of bronchial asthma [2]).

According to the latest GINA version, respiratory function parameters are used to assess risk factors of adverse outcomes and are not considered criteria of assessing disease control. Low forced expiratory volume per second, especially when this parameter is < 60% of the normal value, is considered prognostically unfavorable.

Drug-free therapy

Asthma therapy should involve both drug and drug-free methods. It is important to limit contact with trigger factors of disease exacerbation. Patients should also be recommended respiratory maneuvers – a useful addition to drug therapy despite lowering of the level of evidence of positive effect of respiratory maneuvers on bronchial asthma course in the updated GINA version (from level A to level B) [2, 11].

Table 2. Assessment of bronchial asthma (BA) control level in adults and children (≥ 6 years of age) [3]

BA symptoms in the patient within 4 previous weeks	BA control levels		
	Complete	Partial	None
Diurnal BA symptoms occur more often than twice a week (yes/no)	No symptoms	1-2 aforesisted symptoms	3-4 aforesisted symptoms
Awakening at night due to asthma (yes/no)			
Need in using bronchodilators more often than twice a week* (yes/no)			
Limited activity due to asthma (yes/no)			

Note. * - except for using bronchodilators before physical exercises.

Table 3. Assessment of bronchial asthma (BA) control level in children (≤ 5 years of age) [3]

BA symptoms	BA control levels		
	Complete	Partial	None
Diurnal BA symptoms lasting for more than several minutes occur more often than once a week (yes/no)	No symptoms	1-2 aforesisted symptoms	3-4 aforesisted symptoms
Limited activity due to asthma: runs, plays less than other children; gets tired quickly when walking/playing (yes/no)			
Need in using bronchodilators more often than once a week* (yes/no)			
Awakening at night or nocturnal cough due to asthma (yes/no)			

Note. * - except for using bronchodilators before physical exercises.

Staged approach to therapy

Updated GINA version maintain staged approach to asthma therapy based on frequency and intensity of disease symptoms.

Stage 1 therapy. Symptomatic therapy (SABA) as required. Recommended for patients with rare symptoms (less than twice a week) occurring only in the daytime and lasting a small time (up to several hours). The use of long-acting β_2 -agonists (LABA) for symptomatic therapy without baseline IHCS therapy is strongly discouraged due to high risk of adverse asthma outcome. Peroral β_2 -agonists and theophylline are not recommended to children either as development of side effects due to the use of these drugs outweighs their possible benefits. Given the continuing absence of sufficient data on absolute safety of SABA monotherapy even for patients with rare symptoms, prescription of low IHCS doses to patients featuring risk factors of adverse BA outcome may be recommended as early as on stage 1 of the therapy.

Stage 2 therapy. Low doses of a baseline therapy drug and symptomatic therapy (SABA) as required. The preferred drugs for baseline therapy are IHCS. Leukotriene receptor antagonists are a reasonable alternative, especially for patients with concurrent allergic rhinitis or IHCS intolerance, even though these drugs are less effective than IHCS. Baseline IHCS therapy is recommended to patients with asthma the symptoms whereof manifest themselves only in specific seasons (pollen sensitization) from the time of symptom occurrence and throughout the season, as well as for 4 additional weeks. Preschoolers with virus-induced BA exacerbations may be recommended periodic or episodic IHCS use; however, regular therapy remains the preferred approach. Routine cromone use is discouraged due to their insufficient effectiveness and complicated regimen.

Stage 3 therapy. One or two baseline drugs in combination with LABA as required. The preferred option for adolescents is to use low IHCS doses in combination with LABA, for 6-11-year-old children – medium doses of IHCS (double low IHCS doses) and SABA as required. Addition of leukotriene receptor antagonists to low doses of IHCS as the baseline therapy and SABA as required may be a reasonable alternative. The other, less attractive alternative for over-11 children may be the use of low doses of IHCS and sustained-release theophylline.

Stage 4 therapy. Two or more baseline drugs and symptomatic therapy as required. The preferred combination for over-11 adolescents is the use of low doses of IHCS together with formoterol as baseline and symptomatic therapies or a combination of medium doses of IHCS with LABA and SABA as required. Under-11 children are recommended to refer for a consultation at a higher level establishment. Unlike adults, 6-11-year-old children are not recommended to take theophylline as the baseline therapy. Therapeutic choice for under-5 children at stage 4 is limited to the age-permitted range of drugs used at asthma and, at present, is based only on opinions of experts: GINA proposes considering the possibility of increasing the IHCS dose to the medium level or adding leukotriene receptor antagonists or sustained-release theophylline for several weeks until condition improvement as an alternative. The baseline IHCS dose may be periodically increased in the intermittent mode during exacerbations.

Stage 5 therapy. Refer a patient to a high level third-tier establishment. On this stage, over-6 children with persistent symptoms of asthma and exacerbations despite an adequately prescribed treatment, observance of the correct inhalation technique and high compliance are prescribed immunoglobulin E monoclonal antibody preparation omalizumab. Unlike adults, children are not recommended to take oral corticosteroids and tiotropium.

Therapy choice should respect peculiarities and preferences of the patient and/or his/her legal representatives.

Asthma severity is assessed on the basis of the therapy volume required to maintain control over the disease. Asthma severity may be assessed using treatment results after several months of therapy. This parameter is regularly reassessed subsequently, as asthma severity may modify.

- Mild asthma may be diagnosed in the patients with the disease controlled well by means of stage 1 drug therapy.
- Moderate asthma is well-controlled with stage 3 drugs.
- Severe asthma may be diagnosed in the patients requiring stage 4-5 therapy to control symptoms or the patients with uncontrolled asthma despite an adequately prescribed therapy.

It is recommended to reassess the patient's condition after ca. 1-2 months of primary therapy and every 3-12 months thereafter. Therapy may be adjusted up or down on each stage. The treatment is aimed at maintaining control over asthma by means of the least possible drug load sufficient for maintaining high level of control and minimizing side effects of drugs.

Metered dose inhalers

It is well-known that one of the main problems in achieving asthma control is misuse of inhalers [12-14] and insufficient patient's compliance [2]. That is why it is extremely important to regularly check inhalation technique and, if possible, control drug delivery rate and/or assess the child's and/or his/her legal representatives' compliance to the prescribed therapy. The preferred drug delivery device for under-3 children is a metered dose aerosol inhaler (MDAI) with a spacer and a facepiece; an alternative option is a nebulizer with a facepiece. It is recommended to start using a mouthpiece instead of a facepiece as soon as possible. 4-6-year-old children are recommended to use a MDAI with a spacer and a mouthpiece; an alternative is to use a MDAI with a spacer and a facepiece or a nebulizer with a mouthpiece. Over-6 children are usually able to use almost any kind of delivery devices, although the preference should still be given to a MDAI with a spacer and a mouthpiece. Use of a MDAI with a spacer is a principal condition of quality drug delivery; moreover, a spacer should be antistatic to avoid drug loss due to deposition on device walls. Not all children (especially adolescents) use spacers; according to the

conclusions made by expert groups of specialists from the European Respiratory Society (ERS) and the International Society for Aerosols in Medicine (ISAM), the optimal decision in such cases is to use metered dose dry powder inhalers [15].

Before going to the next asthma therapy stage it is necessary to check inhalation technique and compliance with the prescribed recommendations; check the presence of a concurrent pathology (rhinosinusitis, obesity, gastroesophageal reflux disease, mental disorders, smoking etc.), preservation of action of possible risk factors and in some cases (especially in preschoolers) review diagnosis.

Smaller therapy volume should be considered for patients with well-controlled asthma and stable respiratory function for 3 or more months in the absence of risk factors. IHCS dose reduction by 25-50% at three-month intervals is recommended for most patients.

Asthma exacerbations

Asthma exacerbation therapy has not been changed significantly in the latest GINA version. Its main principles remain the same: repeated prescription of SABA, early use of systemic corticosteroids if primary SABA therapy is ineffective.

GINA-2015 changes concern the obtained proof that SABA administered with a metered dose dry powder inhaler are as effective for treating mild and moderate exacerbations as the previously used delivery means (MDAI with spacers and a nebulizer) [16]. Despite the fact that SABA for metered dose dry powder inhalers are not registered in Russia, this is important in terms of effectiveness of drug delivery to lungs by means of such devices.

Aminophylline and theophylline should not be used for treating bronchial asthma exacerbations as they are less effective and feature a worse safety profile than SABA.

Approaches to asthma exacerbations in preschoolers in the setting of an acute respiratory infection were updated in 2015 as well: routine home use of peroral corticosteroids or IHCS in high doses should be avoided. This recommendation is based on the fact that this age group is susceptible to frequent acute respiratory infections; regular use of systemic corticosteroids or high doses of IHCS increase the risk of development of side effects of these drugs.

GINA-2015 is the first document to allow use of β -blockers in patients with bronchial asthma, although only at acute coronary paroxysms and under extremely careful control by a specialist in order to appraise the risk/benefit ratio of such an intervention in a particular patient.

CONCLUSION

Thus, key aspects of the reviewed and updated approaches to diagnosis and therapy of bronchial asthma in children presented in documents GINA-2014 and -2015 indicate significant progress in the knowledge about this disease. Consensus postulates should be included into national clinical recommendations for optimizing diagnosis and therapy of pediatric patients with bronchial asthma.

CONFLICT OF INTEREST

The authors of this article have declared absence of reportable financial support / conflict of interest.