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Modern approach to pediatric asthma

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Abstract

Background: The article reviews aims to promote the communication between scientists engaged in basic research and clinicians working with children, in order to better understand the mechanism and work together towards an optimal management of this prominent pediatric condition. We reviewed the recent advancements in regards to pediatric asthma related to pathogenesis, diagnostic criteria and differential diagnosis, and peer-reviewed evidence for efficiency of pharmacological and non- pharmacological/alternative/adjuvant treatment; we also emphasize the importance of education of all parties involved in care, outpatient management, age-appropriate involvement of children in their own care, and asthma prevention measures in children. Clinically asthma is characterized by recurrent episodes of wheezing, dyspnea, and cough; at the pathophysiological level the airway wall thickness is increased and involves both smooth muscle and collagen tissue, the mucous glands and mucus production are increased, and the vascularity of the airways is increased, all leading to chronic inflammatory remodeling of the airways and resulting in reduction of lung function.

Conclusions: Asthma among children has been on the rise for decades. With an estimated prevalence of 10-30%, asthma is the most prevalent chronic disease of pediatric population worldwide and one with a large health care burden. The approach to diagnosis and treatment of asthma in children is distinct from adults; so is the management, prevention and the education of parties involved in care. Recently there has been a significant progress in mechanistic understanding of asthma; further, asthma management in children is becoming a top priority.

Key words: asthma, recommendations, pediatric, children, pathogenesis, therapy, management.

Introduction

Asthma is known to humanity since ancient times. The name asthma is derived from ancient Greek meaning gasping or panting. The description of asthma dates back to Hippocrates (460 - 357 BC) who first described asthma spasms, and to Galen (201-130 BC) who defined asthma symptoms and established that asthma was caused by bronchial obstructions. Despite long history, it was believed that asthma is a disease of adults; only with industrialization was acknowledged that asthma also affects children.

Childhood asthma: how big the problem really is?

Based on the largest cross-sectional study from ISAAC Phase Three study, which included 193,404 children aged 6-7 years from 66 centers in 37 countries, and 304,679 children aged 13-14 years from 106 centers in 56 countries, asthma has a prevalence of 10% to 30% in children worldwide (1). With such magnitude, asthma is the forerunner chronic medical condition in childhood worldwide. In US alone, the prevalence of asthma among children more than doubled in less than 2 decades (1980-1996) and has reached an alarming 9.4% in 2008 (2), up from 8.9% in 2005 (2).

Morbidity and mortality from childhood asthma: estimated and hard-to-estimate costs

Health care use for asthma in all ages includes outpatient visits to doctors' offices and hospital outpatient departments, visits to hospital emergency departments (EDs), and hospitalizations (1-3); the pediatric population adds the financial burden from the missed school days, estimated 12.8 million in children 5-17 old, and from days that their parents miss from work while taking care of their children (3). In 2005 in US, children had 7.0 million visits and an outpatient visit rate of 958 per 10,000 pediatric population. Children also had over 754,000 ED visits, at a rate of 103 per 10,000. The ED visit rate was highest among children aged 0-4 years at 168 per 10,000. Among children 0-17 years, there were 198,000 hospitalizations (27 per 10,000). Hospitalizations were highest among children 0-4 years, 60 hospitalizations per 10,000. Among children, asthma deaths are rare (2.3). In contrast, asthma causes significant morbidity and is the most frequent reason for preventable childhood hospitalizations (4). In addition to the sizable costs, there are largely underestimated costs from the psychological burden of asthma on children due to impaired quality of life, long-term health outcomes of childhood asthma during adulthood, and impaired quality of life in caregivers (5).

The face of childhood asthma: age, gender, race, genetic background, socio-economic status, access to and quality of child care and more

Age. Asthma often appears in early childhood, is diagnosed by 3.5 years of age in most of children who will develop childhood asthma and the rate keeps at steady frequency by 5.5 years (1-3). While it is difficult to predict the prospective identification of asthma phenotype and its clinical course, it is currently estimated that 3 out of 4 school-aged children with asthma will have outgrown their disease by mid-adulthood. The risk of persistence of childhood asthma

into adulthood increases with severity, sensitization, exposure to environmental offending agents including smoke, and female gender (7).

Gender. As of 2005, in US asthma prevalence for boys (10%) was 30% higher than for girls (7.8%) (3); it has been reported that hormonal status is important for asthma development, however it remains to be determined which factors contribute to the fact that more adult women are diagnosed with asthma than adult men (8).

Race and population/ethnicity. According to Akinbami LJ et al, at least in US, there are no significant differences in asthma prevalence between race groups (9). In contrast, asthma-related morbidity is higher among black children. Among racial categories, black children are most likely to have activity limitations due to asthma but only if they are economically disadvantaged: 49% of those who were also and poor were limited compared with about 20% of black non-poor, white poor, and white non-poor children (9). Even when access to healthcare is accounted for, as described in a study by Stewart KA et al involving children whose parents were in the military and who therefore had access to health insurance and treatment, black children were more likely to be diagnosed with asthma than either Hispanic or white children (9.6% versus 8.0% and 6.3%, respectively) (10). Black children with an asthma diagnosis also were more likely than Hispanic or white children to have a potentially avoidable hospitalization for asthma (2.6% versus 2.0% and 1.3%, respectively) or for any other medical reason (2.9% versus 2.2% and 1.6%, respectively) (10). Finally, black poor children had the lowest level of ambulatory care use for asthma after accounting for disease severity (9). Besides being linked to race, asthma prevalence in the US varies drastically between diverse US populations/ethnicities (11). In US, asthma prevalence is highest in minorities, including Puerto Ricans, African Americans, Filipinos, Irish Americans, and Native Hawaiians, and lowest in Mexicans and Koreans (12-14). Mortality rates from asthma-related morbidity follow similar trends in all races and ethnicities; response to medication, including Salbutamol, is lower in descendants of Indian and Puerto Rican origin than in African Americans or Mexicans (15,16). Asthma prevalence also differs between populations of the same ethnicity who are born and live in different places (17). US-born Mexican populations, for example, have higher asthma rates than non-US born Mexican populations that are living in the US (18).

Genetic background. There are compiling data suggesting that the genetic background may be implicated in susceptibility, and severity, of asthma. Studies from Thomsen SF et al showed that the risk of asthma in the co-twin of an affected twin was higher in mono-zygotic than in di-zygotic twins (19). The risk of asthma in the co-twin decreased with increasing age at onset of asthma in the index twin; the effect was attenuated in di-zygotic twins relative to mono-zygotic twins. According to these studies, genetic factors explain ~34% of the variation in the age at onset of asthma, and environmental factors account for ~66% (19).

Current literature indicates that asthma signs and symptoms are more common in those with alpha-1 antitrypsin deficiency (AATD) (20), or mutations in *DENND1B*, a protein that interacts with the tumor necrosis factor (TNF) α receptor and represses inflammatory-cell TNF-receptor signaling (21), ADAM33 (ADAM metallopeptidase domain 33, a disintegrin and metalloproteinase domain 33) (22) or in sphingosine-1-phosphate receptor (S1PR1), a regulator of vascular permeability and an essential participant regulating lung vascular integrity and responses to lung inflammation (23). Children with CHIT1 mutations are at higher risk for severe asthma with fungal sensitization (24). The genome-wide association studies (GWASs) revealed an asthma-predisposing SNP signature in interleukin 1 receptor- like 1/ interleukin 18 receptor 1 (IL1RL1/IL18R1), dipeptidyl-peptidase 10 (DPP10), phosphodiesterase 4D (PDE4D), V-myb myeloblastosis viral oncogene homolog (MYB), PDE10A, IL33, and especially protein tyrosine phosphatase, receptor type D (PTPRD) genes. In addition, rs10938397 near glucosamine-6- phosphate deaminase 2 (GNPDA2) and protein kinase C alpha (PRKCA) were top gene SNPs common among both increased BMI (obesity) and asthma (25). In contrast, TLR2/rs7656411 TT variant homozygote had a significantly reduced risk of asthma when compared with those with the GG wild- type homozygote. Furthermore, a positive association was observed between the T allele of rs2381289 in TLR6 and allergic rhinitis in asthma, while the A allele of rs11466651 in TLR was negatively associated with allergic rhinitis (26). MHC haplotype has significant effect on CD8 cell response and is an important determinant of the outcome of neonatal RSV infection; it remains to be determined if these factors are important for virus-dependent sensitization and development of asthma (27). Collectively these data suggest a role for innate immunity and inflammation in asthma.

Socio-economic status. The incidence of asthma is highest among low-income populations; such disparity is observed in US and worldwide (9, 28). Asthma deaths are most common in countries with low income and in neighborhoods with limited income and increased frequency of ethnic minorities. Given the fact that asthma has been strongly associated with the presence of household insects, including cockroaches; and the most prevalent presence of these insects in low-income neighborhoods, it is also indicative of association between low socio-economic status and asthma. It remains to be determined if limited resources and/or limited access to medical care can account for the low incidence of and treatment quality for asthma that varies significantly among different racial groups (29). For example, poor African Americans are less likely to receive outpatient treatment for asthma, more likely to require an emergency room visit or hospitalization for their asthma symptoms and have higher likelihood as a race of dying from an asthma attack compared to whites. The prevalence of "severe persistent" asthma is also greater in low-income communities than those with higher income (29, 30).

Access to and quality of child care. A study by Gurka et al

shows that the number of children in the child-care environment when the child was a toddler is significantly associated with odds of asthma, even after adjusting for respiratory illnesses and other risk factors (31). The fewer the children are exposed to triggering agents as toddlers, the higher the probability of persistent or late-onset asthma by age 15 (31).

Epigenetic. It is well established that maternal, and even paternal, health status, and their habits, such as consumption of alcohol or tobacco, may influence the health of the off-spring; such connections were closely established for low birth weight infants, immunity, and obesity. More recently, Folic acid taken in supplement form in late pregnancy was associated with an increased risk of childhood asthma at 3.5 years and with persistent asthma (32).

Pathophysiology of asthma

Asthma is characterized by inflammation and hyper-reactivity of airway in response to triggering agents that include allergens such as pollen or mold, viral respiratory infections, or other stimuli/irritants, such as tobacco smoke, cold and exercise. How the irritants trigger asthma is less well understood; in case of allergens and viruses, they are inhaled and taken up by the epithelial and immune cells in the upper airways and in the lungs. Upon exposure to triggers, a complex immune cascade is initiated in both innate and adaptive immune cells (33-37). Innate immune cells, including macrophages and dendritic cells, are activated and attempt to eliminate the trigger by degradation while producing pro-inflammatory signals, including cytokines and chemokines. In addition, innate immune cells process the triggering molecules and present them to adaptive immune cells, including T and B lymphocytes (34). Lymphocytes attack the infected/damaged cells in the airways, by cytokines/chemokines, and by secreted antibodies. It is believed that Th2 is predominant in asthma with production of IL-4, IL-5, IL-9, and IL-13. IgE production by B cells is most detrimental in asthma. Altogether, these complex immune reactions promote inflammation, which further activate the release of pro-inflammatory mediators from and recruitment of mast cells, macrophages, eosinophils and other immune cells in the airways (35). It is this complex response that collectively causes injury of the airway epithelium, prolonged contraction of smooth muscle, edema and glandular hypertrophy followed by exaggerated secretion of mucus; inflamed airways become more narrow and obstructed and are further hyper-responsive to subsequent stimuli (35,36). Airway obstruction can develop suddenly or gradually and accounts for asthma symptoms. In the long run, if the inflammation and hyper-responsiveness persist, a remodeling of the airway occurs. Airway thickening of all components of the airway wall (inner, outer, and total) occurs in long-term asthma from the epithelial hypertrophy, mucus metaplasia, increased muscle mass from myofibroblast hyperplasia, and connective tissue deposition followed by sub-epithelial fibrosis (33). All these events contribute to progressive decline in lung function and continuous sensitivity to trigge-ring agents in asthma (33-37) (fig. 1). However, it is wise to acknowledge that our understanding of the mechanisms of asthma is yet minimal, even with the fast pace of recent discoveries in the areas of environmental biology, immunology, omics (genomics, proteomics, inter-

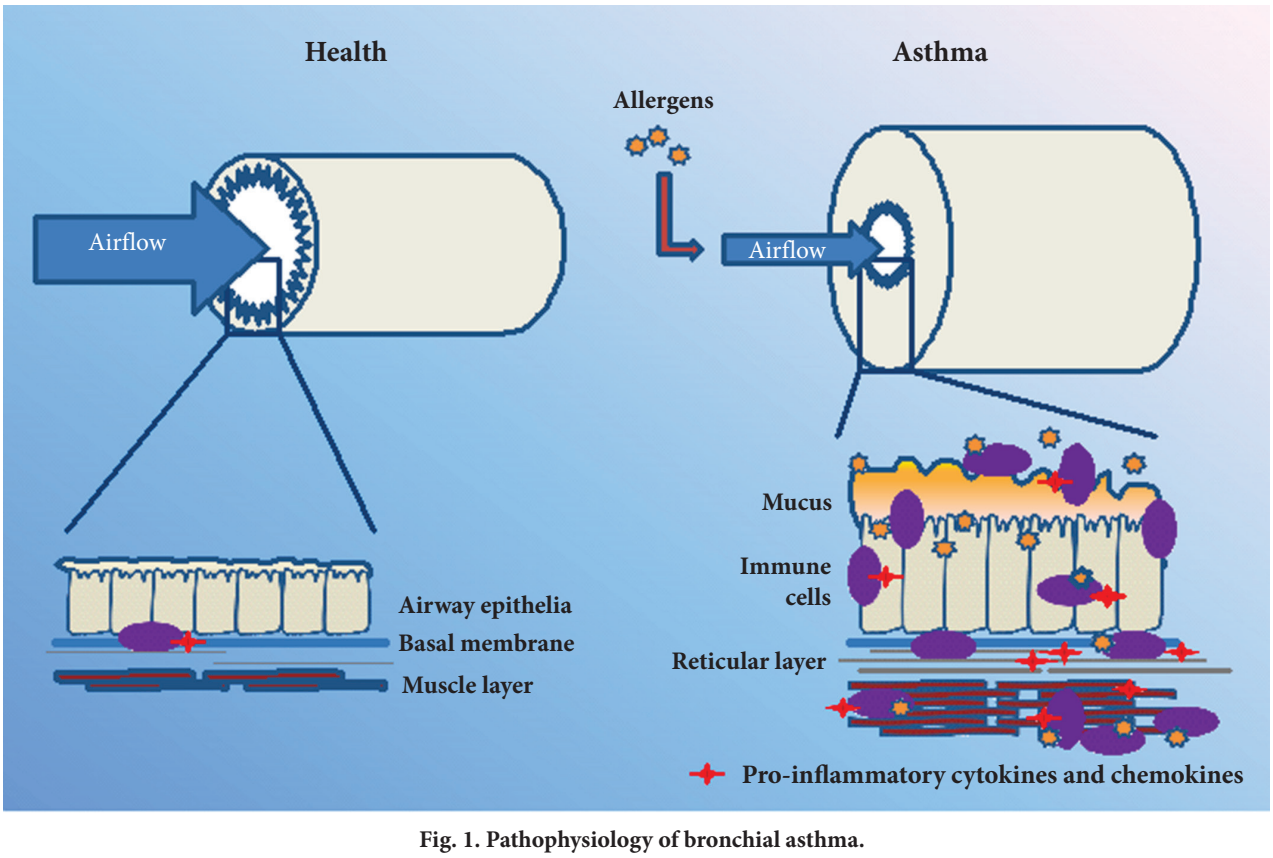

Fig. 1. Pathophysiology of bronchial asthma.

actomics) and our symbiosis with airway, skin and gut microbiota. While we managed to identify individual players in many of the processes involved in asthma, we still lag behind in our ability to connect all the discoveries in a bigger picture of asthma. In these conditions, extensive research is needed, more than ever, to fully understand the pathogenesis of asthma, with special focus on early pediatric age.

Clinical manifestations of asthma in childhood

Clinically asthma is characterized by recurrent episodes of wheezing, shortness of breath, cough and chest tightness. Symptoms are often worse at night or in the early morning, and often occur in response to exercise, cold air or triggering allergens.

The diagnostic process of asthma

Accurate diagnosis is critical in pediatric asthma; unfortunately in pediatric population additional difficulties are often encountered in the diagnosis process, including the intermittent and non-specific clinical presentation, limited ability of the patient caregiver to present a detailed history of the disease in the proband and health status in related family, etc. Nevertheless, several clues are available to aid the diagnosis of asthma in children. First, asking the right questions in a case when asthma is suspected helps: history of cough occurring with or without colds which are aggravated at night, recurrent wheezing, dyspnea and chest tightness, some or all of which are precipitated or aggravated by physical activity, exposure to house dust, smoke, animals with fur, nature (grass, pollens) or alternating emotions are suggestive of asthma. Second, collection of disease history from the proband can be employed in children as early ages of ~5 years old; it is important to note what their individual perception of symptoms is and how they define the effects of their disease on their quality of life. Third, family history is of great importance: asthma, eczema, eosinophilia, allergies, smoking may suggest of origins of asthma. Fourth, a focused physical exam of a child is warranted when asthma is suspected: include respiratory tract, chest, and skin, but do not overlook the general health (nourishment status, neurological and musculo-skeletal status, intellectual status, age-specific milestones).

Diagnostic criteria of asthma in childhood

Currently there is no precise diagnostic test for asthma. Similar to good old days, when medicine was solely based on the ability of the physician to recognize a disease by a combination of clinical symptoms, asthma is largely a symptom-based diagnosis today. The Expert Panel from Asthma Education and Prevention Program (NAEPP) of the National Heart, Lung, and Blood National Institute has issued the G3 report in 2007 outlining the Guidelines for the Diagnosis and Management of Asthma (38). In this report the experts recommended that essential elements in asthma evaluation include the history, symptoms, physical examination, and assessment of quality of life, as well as therapeutical trial with medications are key in the diagnosis of asthma in 0–4 years of age group, while 5–11 years of age group is to be analyzed as adults, based on detailed medical history, physical exam focusing on the upper respiratory tract, chest, and skin (including identification of episodic symptoms of airflow obstruction or airway hyperresponsiveness, airflow obstruction), and exclusion of alternative diagnoses. Spirometry to demonstrate obstruction and assess reversibility was recommended in children 5 years of age or older; reversibility was determined in these guidelines either by an increase in FEV1 of ≥12 percent from baseline or by an increase ≥10 percent of predicted FEV1 after inhalation of a short-acting bronchodilator. It is thus clear that the NAEPP recommendations, listed in table 1, do not fully distinguish between adults and children older than 5 years of age. NAEPP specifies that spirometry is needed to establish a diagnosis of asthma; further, spirometry is recommended at the time of initial diagnosis, after treatment is initiated and symptoms are stabilized, whenever control of symptoms deteriorates, and every 1 or 2 years on a regular basis.

Table 1

The NAEPP recommendations for diagnostic criteria of asthma

- Wheezing-high-pitched whistling sounds when breathing out. Lack of wheezing and a normal chest examination do not exclude asthma.
- History of any of the following:
  - o Cough, worse particularly at night
  - o Recurrent wheeze
  - o Recurrent difficulty in breathing
  - o Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
  - o Exercise
  - o Viral infection
  - o Animals with fur or hair
  - o House-dust mites (in mattresses, pillows, upholstered furniture, carpets)
  - o Mold
  - o Smoke (tobacco, wood)
  - o Pollen
  - o Changes in weather
  - o Strong emotional expression (laughing or crying hard)
  - o Airborne chemicals or dusts
  - o Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient

Table 2

Diagnostic criteria of asthma used by the British Thoracic Society

BTS recommendations are based on the 'response to therapy' approach: a positive response to treatment, assessed as reversibility of airway obstruction, is considered diagnostic of asthma.
BTS recommends that airflow measurement is diagnostic when:

- ≥20% difference on at least three days in a week for at least two weeks;
- ≥20% improvement of peak flow following treatment, for example:
  - o 10 minutes of inhaled β-agonist (e.g., salbutamol);
  - o six weeks of inhaled corticosteroid (e.g., beclometasone);
  - o 14 days of 30 mg prednisolone.
- ≥20% decrease in peak flow following exposure to a trigger (e.g., exercise).

The British Thoracic Society (BTS) recommends the 'response to therapy' approach for asthma diagnosis (39). A positive response to treatment, assessed as reversibility of airway obstruction, is considered diagnostic of asthma. Further, BTS recommends airflow measurement with a peak flow meter or spirometer. The BTS diagnostic criteria for asthma are listed in table 2; similar to NAEPP recommendations (tab. 4), the BTS recommendations do not fully distinguish between adults and children.

Spirometry

Spirometry is necessary to confirm the diagnosis of asthma, but can be also useful in assessing the degree of congestion. Two conditions are to be assessed: baseline and post-inhalation of a short- acting beta agonist (SABA); two parameters are to be measured during spirometry, including forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), and the FEV1/FVC ratio is to be calculated. Due to the great need for cooperation from the patient during spirometry, this procedure is recommended only for children older than 5 years old. Disproportionate limitation of FEV1 compared to FVC, indicated by decreased FEV1/FVC ratio, is diagnostic of obstructive disease; the response to SABA is indicative of the reversibility of airway obstruction. If the post-SABA FEV1 rises with more than 200ml or +12% compared to the baseline, the airway obstruction is considered reversible. If the spirometry results are not conclusive and the diagnosis of asthma is still suspected, a bronchial provocation with histamine or methacholine may be employed. This test is limited to those with >65% preserved FEV1; a -20% FEV1 post-stimulation is indicative of asthma.

Differential diagnosis of asthma

There are several diseases that are often misdiagnosed as asthma; among the first criteria to use for a differential diagnosis of asthma in childhood is the child's age. In infants the differential diagnosis task is relatively easy, because asthma is seen relatively rarely in this age group and it is often considered as a differential rather than the primary diagnosis. In older children, differential diagnosis of asthma often requires thorough investigation. Nevertheless, excellent diagnostic skills are required from the physician in order to accurately diagnose asthma at all ages.

In *an infant*:

1. Transient infant wheezing occurs early in life; however, it is without clear ties to atopy but with clear relationship to maternal smoking.

2. Milk aspiration, due to neurological problems or anatomical defects, is usually associated with feeding, and if left untreated, is associated with lung infections and developmental delays.

3. Structural abnormalities of the bronchial tree (tracheo-, broncho-malacia) are often manifested shortly after birth and only pose difficulty in differentiation when are manifested later in life.

4. Cardiac failure associated with congenital or acquired heart diseases is rarely a problem for asthma differentiation at any age.

5. Inhalation of foreign body can occur in any age and is often presented with an acute onset and shows differential air entry in addition to wheezing; when not removed promptly it may be mistaken with asthma and needs a detailed history, thorough examination and imaging.

6. Vascular rings/laryngeal webs. Vascular rings (VR) are caused by the abnormal persistence of embryonic tissue that comprises the aortic arch because of double aortic arch (50-60%), right aortic arch with an aberrant left subclavian (12-25%), or pulmonary artery sling. VRs often present with a clinical picture of tracheo-esophageal compression, wheezing and stridor or sudden apneic and cyanotic spells; they are often diagnosed as recurrent bronchiolitis. *Laryngeal webs* are caused by failure of normal embryonic tissue regression; depending on the severity of anatomical defect, the LW often present with varying degress of respiratory distress ranging from severe subglottic stenosis diagnosed at birth with respiratory failure to identification in older children with weak cry, horseness and recurrent croup. Instrumental investigation is useful for the differential diagnosis in these cases: laryngoscopy and lateral neck films are useful for LW, while barium swallow and MRI are often used for VR.

In *older children*, the differential diagnosis of asthma requires a more extensive investigation as candidate diseases are more abundant.

1. *Genetic disorders*, such as cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) should be always on the watch. *CF* may be suspected if the recurrent wheezing is associated with failure to thrive. *PCD* may be suspected in infancy, when supplemental oxygen is needed early postnatally, or later in life when present with wheezing and cough; however it stands apart from asthma due to its association with recurrent otitis, sinusitis and situs inversus.
2. *Viral infections* accompanied with bronchiolitis may result in a lingering wheezing and dyspnea.
3. *Eosinophilic lung disorders (ELD)*, including allergic bronchopulmonary aspergilosis, can be often mistaken with asthma, however, in ELD the serum IgE is often elevated, along with positive imaging picture (chest infiltrates) and positive skin prick test to Aspergillus antigen.
4. *Mental health problems*, such as anxiety-associated hyperventilation, depression and panic disorders, are often seen on older children and the triggering factor is clearly not of allergic nature; little or no wheezing is present and the spirometry parameters lack FEV abnormality.
5. *Vocal cords dysfunction* (VCD) is rare in children however, it may present with episodic, abruptly starting and stopping wheezing, cough and severe difficulty breathing; unlike asthma, where inspiratory flow is obstructed, the VCD is associated with a preserved expiratory loop and flow and flattened expiration.
6. *Churg-Strauss vasculitis (CSV)* may be mistaken with asthma, especially at the early disease stages. However, unlike asthma, CSV is accompanied by anemia, persistent

eosinophilia, raised erythrocyte sedimentation rate and positive anti-neutrophil cytoplasmic antibody in 30-50% of patients; the definitive diagnosis of CSV requires biopsy of the lungs and other affected organs.

7. *Enlarged lymph nodes or tumors (head and neck, mediastinal)* can press the respiratory pathways to mimic asthma; targeted evaluation of these conditions should be performed in children when both inspiratory and expiratory flows are affected, even if no symptoms of infection/inflammation or cancer are observed.
8. *Exertional dyspnea (ED)* may be the most challenging to distinguish from asthma, however in ED symptoms are present exclusively during exercise. A particular challenge in children is the differential diagnosis of exertion asthma (EA).
9. *Pulmonary embolism (PE)* is seen in ever younger adults and may occur in teens. While difficulty breathing in PE may be mistaken with asthma, a thoroughly collected anamnesis, a rapidly progressing clinical course with acute onset of symptoms and rapid deterioration of respiratory function, aided by indicative imaging investigations are key for differential diagnosis.

Several co-morbidities and triggering factors that are often difficult to separate from asthma; these are usually present in older children.

1. *Diseases of upper airways*, such as chronic rhinosinusitis and nasal polyps, are frequently associated with severe asthma. Nasal congestion/obstruction, purulent nasal and/or retropharyngeal discharge, facial pain or pressure, hypo- or an-osmia, ear pressure/fullness and halitosis despite adequate dental hygiene, are suggestive, while nasal endoscopy and imaging of the nasal cavity and sinuses are confirmative of rhinosinusitis and nasal polyps (40). Medical or surgical treatment of upper airways diseases have been proven useful in managing asthma in adults. Conversely, patients with severe asthma should be systematically evaluated for upper airways diseases.
2. *Gastrointestinal reflux (GERD)* is common in patients with asthma however rarely causes severe asthma symptoms. Regurgitation, dysphagia, heartburn, odynophagia, excessive salivation, nausea, chest/upper abdominal pain, chronic cough, laryngitis, and erosion of dental enamel are suggestive of GERD. Although a 24hrs pH monitoring is needed to confirm the GERD, most physicians prefer an empiric therapy trial with proton pump inhibitors.
3. *Obesity* is a co-morbidity factor for childhood asthma. According to Sulit et al, childhood obesity raised the risk for asthma by 1.8 times and the risk of wheeze 1.6 times (41). It is yet to be identified if the association between asthma and obesity is causal. It is interesting, however, that calorie restriction improves clinical findings and reduces airway inflammation in overweight adults with moderate asthma and has long-term health benefits, including improvement of asthma symptoms (42,43); such events are expected but yet to be defined in pediatric population.

Management of childhood asthma: severity assessment

The assessment of severity is among the most difficult tasks in managing pediatric asthma. The criteria for distinguishing the severity stages in acute and interval asthma are listed in tables 3 and 4, respectively. The golden rule while assessing the severity of asthma in children is to observe often and act promptly; ultimately preventing progression of severity is highly-desired an achievement.

Management of childhood asthma: pharmacological treatment

Asthma is both an easy and a difficult disease: in the former scenario the response to therapy is fast and complete;

Table 3

Severity assessment criteria for acute asthma episodes

Manifestation/Symptom		Severity		
		Severe-to-life threatening	Moderate	Mild
Observational /Subjective	Ability to talk	Unable to speak or separate words	Phrases	Sentences
	Consciousness	Agitated, confused/drowsy or Absent	Normal	Normal
	Central cyanosis	Present	Possible	Absent
	Wheezing	Quiet	Moderate to loud	Variable
Objective	Oxymetry (SaO2)	<90%	90-95%	Above 95%
	Pulse rate	>200/min	100-200/min	<100/min
	FEV1	Unable to perform spirometry or <40% predicted value	40-60% predicted value or previous baseline value	>60% predicted value or previous baseline value
	PEF	Unable to perform or <40% predicted value	40-60% predicted value or previous baseline value	>60% predicted value or previous baseline value

Table 4

Severity assessment criteria for interval asthma

Severity	**Intermittent**		**Persistent**		
	Infrequent	Frequent	Mild	Moderate	Severe
Day-time symptoms between exacerbations	None	None	>1/week but not every day	Daily	Continual
Night-time symptoms between exacerbations	None	None	<2/month and not every week	>1/week	frequent
Exacerbation	Brief, mild, occurs every 4-6 weeks	>2/month	<2/week Affects activity and/ or sleep	>2/week Restricts activity and/or affects sleep	Frequent Restricts activity and/or affects sleep
FEV_1 or PEF	>80% predicted value or previous baseline value	At least 80% predicted value or previous baseline value	At least 80% predicted value or previous baseline value	60-80% predicted value or previous baseline value	<60% predicted value or previous baseline value
PEF variability	<20%	<20%	20-30%	<30%	<30%

however, when the response to therapy is poor, asthma becomes a difficult disease to treat and even more difficult one to manage long-term. Management of asthma depends on the severity and the disease stage at which the medical professional encounters the child.

In *acute asthma*, the assessment of severity (tab. 3) will precede and largely determine the treatment; these children should be assessed promptly and in a calm/comfortable atmosphere, in order to prevent agitation and thus worsening of the respiratory insufficiency. The pharmacological treatment, described in detail in table 5, is aimed at reversing/ managing the bronchial constriction and airway inflammation and limiting mucus production. The children with acute asthma should be accommodated in the best-possible psychologically-comforting and temperature-regulated environment and should be monitored often. Inhaled oxygen, b2-agonists, and anticolinergics, and systemic (per os) corticosteroids are used in mild and moderate asthma attacks, their doses are dependent on age/body weight. More severe asthma attacks require more energetic measures towards decreasing the airflow resistance and enhancing airway penetration achieved with heliox and i/v bronchdialators, including salbutamol, aminophilline and magnesium sulphate, and aided by leukotriene receptor antagonists. The therapy is considered efficient when the patients oxygenation is maintained >95%, the symptoms subside and the respiratory parameters are restored. Alternative and adjuvant therapies and psychotherapy are rarely considered during the management of acute episode of asthma in a child.

In *interval asthma*, the management is aimed to maintenance of good control/ remission (defined as lack of symptoms, lack of limitations to activities and sleep, early morning symptoms, exercise induced cough or wheeze, low frequency of bronchodilator use, preservation of lung functions) and prevention/limitation of recurrences/exacerbations (by desensitization to allergens, prevention of inflammation/remodeling, limitation of therapies and their side effects). The frequency of acute episodes and any chronic symptoms should be reviewed often and action should be initiated promptly. In terms of pharmacotherapy, the first choice should be given to inhaled corticosteroids; spacer devices should be used at all ages, even in younger children in whom use of low volume spacer device with a well-sealing face mask may be needed. In addition, allergen immunotherapy, alternative anti- inflammatory agents (macrolides, xantines, ketotifen) should be considered, when indicated. A key component of interval asthma management is the non-pharmacological intervention, including diet, managed physical activity, and healthy life style. Preventive treatment should be initiated if there are frequent acute episodes or chronic symptoms (more than one disturbed night per week, difficulty participating in physical activities, or bronchodilator use on more than one day per week).

In a nut-shell, the approach to asthma therapy in childhood is on step-by-step nature, as detailed in figure 2. The therapy is administered on sliding scale basis depending on the severity of symptoms, should be tapered as soon as the symptoms subside, and should aim to a symptom-free period during which asthma is considered as well controlled. As with many chronic diseases, in which cures are not yet available, a sustained remission is the target of asthma management.

Management of childhood asthma: management plan

Children with asthma usually see a healthcare provider every one to six months to monitor the child's symptom severity and frequency and response to treatment. If asthma control has been adequate for at least three months, the asthma medication dose may be decreased. If control is not adequate, the medication schedule, delivery technique, and trigger avoidance will be reviewed, and the medication

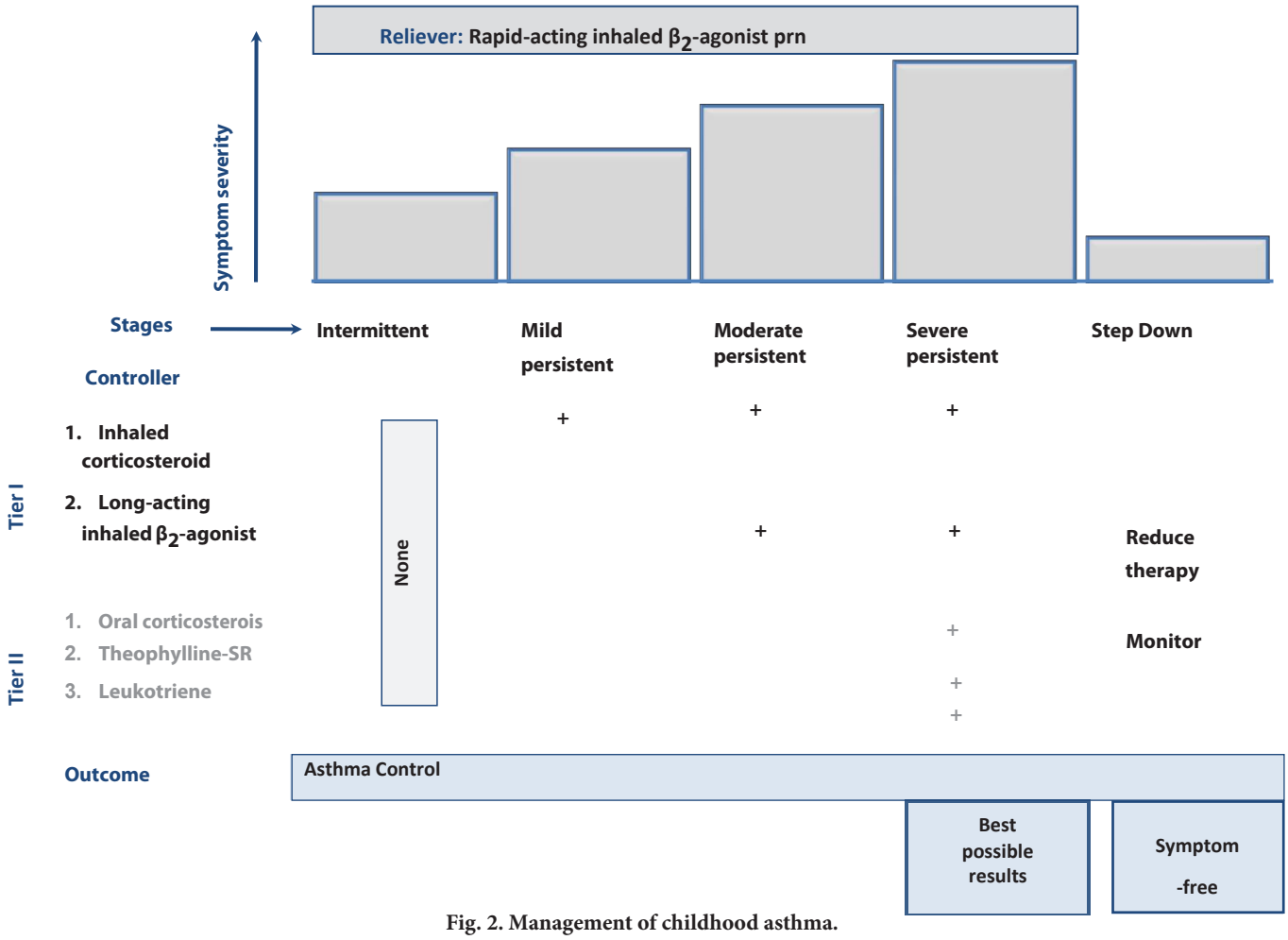

Fig. 2. Management of childhood asthma.

dose may need to be increased. Asthma management goals in children are: symptom free with near normal PFTs; sleep and exercise without asthma symptoms, prevent exacerbations, and minimize medication side effects; none of these is possible without an adequate compliance with the management plan.

National Asthma Education and Prevention Program Guidelines recommend a multimodal, chronic care approach to asthma (38). In this context, the most important component of the management of children with asthma is a specific, customized plan aimed to proactively monitor, identify symptoms in a timely fashion and manage symptoms that involves the caregiver, the child, if sufficiently old, and the medical professional. The treatment plan should be discussed, understood, and agreed upon by all involved parties; the plan should be written down, available at all time for review and adjusted according to changes in symptoms in a timely fashion (48). The healthcare provider may also recommend keeping a daily asthma diary when symptoms are not well controlled or when starting a new treatment; a periodic diary may be recommended for children who have stable symptoms and whose medications have not changed recently.

Management of childhood asthma: challenges for all involved parties

There are challenges for all the involved parties as it relates to following the management plan of a child with asthma; these are related to the age and individual characteristics of the child with asthma, availability and quality of the caregiver, access to medical care, environmental conditions.

The caregiver has to be someone who understands the importance of reducing the child's exposure to allergens, capable of pro-active monitoring the early appearance of the symptoms, and diligent with administering/supervising the therapy of asthma in an outpatient setting. The most often encountered challenges for caregivers are poor socioeconomic status and restricted financial means, leading to inability to protect the children from exposure to allergens, and thus dealing with a never- ending vicious circle of disease progression. In acute asthma exacerbations, the ability of the caregiver to recognize the symptoms and their ability to make arrangements for the delivery of the child to medical care facility in a timely fashion is critical. In interval asthma management, the most challenging task of the caregiver is to prolong an exacerbation-free period along with a healthy life style with age- appropriate activities. The most challenging of all tasks for caregivers is to cope with the specific life style that an asthmatic child brings into the family, all in an efficient yet gracious, cheerful and loving manner.

The children should be encouraged to participate in their own care, as soon as they are sufficiently old to understand the goals and the management plan. Younger children need

to be protected from the symptom-triggering environmental exposure and educated to keep calm upon exacerbations, as stress exacerbates asthma attacks (49). Older children can monitor and identify their symptoms in a timely fashion and even responsibly manage their symptoms with prescribed pharmacological agents. Older children are often tempted by outdoor activities where they can be exposed to cold, athletics with strenuous physical activity, interactions with their peers in crowded, enclosed and thus germ-spreading environments, all of which precipitate asthma symptoms; thus, they need close coaching of their daily lives in order to successfully manage their asthma.

The Medical Professionals are often challenged with difficult differential diagnosis of asthma, especially at extreme childhood ages, rapid progression of the severity of asthma exacerbations, poor management of the diseases requiring ever in need for adjustment pharmacological therapy and insufficient time for outpatient management/follow-up. It is important to stress the need for a follow- up in this particular disease at any stage of care: scheduling an appointment after an emergency department visit increases the likelihood that urban children with asthma would follow up with a PCP (50). Fifield J. et al reported in a recent paper that redesigned medical support is the key to asthma management in children (51). By providing quarterly well-asthma visits using structured visit forms, community health workers for outreach and follow-up, a Web-based disease registry for tracking and scheduling, and a provider education package, the medical professionals have a great potential to truly follow the multimodal, chronic care approach recommended by the National Asthma Education and Prevention Program Guidelines (38,51). Indeed, when intervention sites were given an additional Web- based, computerized patient-specific provider feedback system that produced a guideline-driven medication assessment prompt, the asthma control improved significantly for each of the following visits, suggesting that practice redesign can improve provider adherence to treatment guidelines as well as patients' asthma control (51).

Management of physical exercise in childhood asthma

The physical activity is not to be avoided in children with asthma; moreover, it is to be encouraged, and aim to be of age-appropriate strenuous and symptom-free. In preventing asthma exacerbation upon physical exercise, it is recommended to consult a medical professional before start for comprehensive assessment and thorough planning, start any regimen slowly, keep continuity or warm up gradually at the beginning of each session, avoid cold weather, protect the airway by warming the inspired air. In those who cannot fully comply with these recommendations due to their geographical location or nature of exercise, administer 1-2 puffs of quick and short acting beta agonist (SABA) 5 minutes before starting to exercise.

Management of childhood asthma: adjuvant and alternative treatment

Adjuvant therapy aims to provide support to asthma management in addition to the basic therapeutic regimen. A relatively new approach to long-term care for patients with asthma is the blocking of IgE with monoclonal antibodies (52). Detailed studies of efficiency of such approach in pediatric populations are underway; however, this is not a first-line therapy that will only work in severely atopic patients. In the newer vision of asthma therapy, the inhaled steroids are now recommended in children older than 5 years with persistent asthma; leukotriene modifiers have shown only marginal benefit and are not recommended as first-line therapy or add-on therapy (53).

Alternative medicine (AM) ("holistic", "unconventional", "complementary") includes a broad range of treatments and practices that have not gained wide acceptance in the traditional medical community and so are not considered standard medical treatment. While used in as many is ¼ of adults with asthma (54) and suggested to be useful for asthma control, the alternative medicine use in children is limited. A study by Torres-Llenza et al revealed that alternative medicine use among Quebec children with asthma remained modest (13%), with vitamins, homeopathy and acupuncture being the most popular modalities (55). AM use was associated with preschool age, was highly correlated with ethnicity and episodic asthma. More importantly, AM was also associated with poor asthma control (55). The efficiency of AM in childhood asthma remains to be identified.

Differences between pediatric and adult asthma

For the general practitioners who do not deal with pediatric asthma on daily basis, it is important to summarize the differences between the pediatric and adult asthma. More recently Bush and Menzies- Gow (56) pointed to the age-related variation of asthma phenotypes and classified these age-specific differences based on:

a) Phenotypes of wheezing: often encountered during the first year of life, many remit in the second year of life, and the children who remit do not have later-onset wheeze.

b) Gender/atopy bias: children with severe asthma have no gender bias and are highly atopic, in contrast to the female-preponderant, non-atopic bias seen in adults.

c) Lung function: unlike adults, children with severe asthma have relatively well-preserved lung function.

In terms of pharmacological treatment strategy, children younger than 5 years of age are more difficult to diagnose, treat and manage and require specific approaches; children older than 5 years of age are treated similar to adults, with planned management according to diseases severity and with medication doses corresponding to body weight.

Recent discoveries in asthma research field that promise translational advancement

While avoidance of allergens is often recommended as a primary prevention measure, this is often not possible, not feasible or not effective especially in children. Thus, new preventive measures are needed; in this context measures that aim at naturally occurring mechanisms that might normally limit the development of immune reactions, inflammation and tissue remodeling are most desirable.

Most recently there are several research discoveries that

Table 5

Pharmacotherapy of acute asthma episode

Action	Time-line	Mild episode	Moderate episode	Severe	Life-threatening episode (critical)
Hospitalization	Immediately	Usually not needed	May be needed	Usually needed; may need intensive care	Needed, intensive care
Observation	Immediately	Continuous during the 1st hour, assess after 20 min post- treatment	Continuous during the 1st hour, assess after 60 min post- treatment	Continuous, assess often as needed	Continuous, assess often as needed
Oxygen	Immediately	As needed, monitor SaO2	As needed, monitor SaO2	Required, monitor SaO2	Required, monitor SaO2
Heliox (helium/ oxygen mixture)	Immediately	No	No	May be considered	
SABA (short- acting B2 agonist) Salbutamol (100ug/ puff)	Immediately	Age <6yo: 4-6 puffs; Age >6yo: 8-12 puffs	Age <6yo: 6 puffs; Age >6yo: 12 puffs	Age <6yo: 6 puffs, 3 times during the 1st hour; Age >6yo: 12 puffs, 3 times during the 1st hour	All ages: Nebulizer
	Review in 20 minutes	Give every 1-4 hrs, as needed	If inadequate response: -repeat 2 more times at 20 min intervals -give every 1-4 hrs thereafter	If no effect , bolus IV salbutamol (15um/kg) over 10 minutes, then 1ug/kg/ min thereafter	If no effect in 20 min, bolus IV salbutamol (15um/kg) over 10 minutes, then 1ug/ kg/min thereafter
Ipratropim (20ug/ puff)	Immediately	Not necessary	Optional	Age <6yo: 2 puffs; Age >6yo: 4 puffs	All ages: Nebulizer: Continuous: Every 20 minutes, 3 doses during the 1st hour or use in nebulizer
Corticosteroids	Immediately	Usually not necessarily. Consider depending on the clinical dynamics	Oral prednisone (1mg/ kg) daily for up to 3 days	Oral prednisone (1mg/kg) daily for up to 5 days. Consider IV methylprednisone.	Methylprednisone IV (1mg/kg) every 6 hours on 1st day, every 12 hrs on 2nd day, and daily thereafter.
Magnesium	During the first hour	No	No	Magnesium sulfate 50% 0.1 ml/kg (50mg/kg) over 20 min, than 0.06 ml/kg (0.06mg/ kg) to achieve target serum 1.5-2.5 mM/L	
Aminophylline	Usually after the first hour assessment	No	No	Only in intensive care: loading dose 10 mg/kg; maintenance dose: 1.1 mg/kg/hr if <9yo, and 0.7 mg/kg/hrs if >9yo.	

look promising in terms of taking advantage of the innate immune responses as means to manage asthma. To date, most researchers in asthma field agree with the "hygiene hypothesis" of asthma and attempt to employ innate immunity- mediated approaches to modulation of adaptive immunity as means to manage asthma. Innate immunity (macrophages, dendritic cells) recognizes pathogen-derived molecules by sensing specific patterns in their structure via Pattern Recognition Receptors (PRR) (34-37). The microbe-specific molecules that are recognized by a given PRR are called pathogen-associated molecular patterns (PAMPs), they alert the innate immune cells to bacterial carbohydrates (e.g. lipopolysaccharide or LPS, mannose), nucleic acids (e.g. bacterial or viral DNA or RNA), bacerial peptides (flagellin), peptidoglycans and lipotechoic acids (from Gram positive bacteria), *N*-formylmethionine, lipoproteins and fungal glucans. PRRs that sense endogenous stress signals are called danger-associated molecular patterns (DAMPs); they sense substances released by stressed or dying cells, including uric acid, heat shock proteins etc.

All these receptors trigger production of pro-inflammatory cytokines and initiate, maintain, and participate in resolution of inflammation. At experimental level, it is possible to employ innate immune tolerance (57-59) or adaptive immune responses (60-63) to control asthma mechanisms; it remains to be determined if these findings have translational value. Even with the promising progress of research, the question remains: can manipulation of immune system aid asthma management?

Unequivocally yes, because inflammation is key to pathogenesis of asthma; however, it is to be noted that manipulation of immune system, along with identification of genetic conditions, and modulation of environmental factors will be needed in order to provide personalized therapy of asthma to children.

Future directions

Several research directions are emergent, in the light of ever-growing number of asthma- affected children:

1. Detailed understanding of the processes of sensitization, inflammation, airway reactivity and remodeling is emerging in order to arrive to a sound prevention and much needed pathogenesis-based treatment asthma. In this context, we foresee that the need for research of allergens, developmental immunology, airway microbiota and omics (genomics, proteomics, interactomics). While this type of research is expected to yield data useful for asthma in general, age-specific characteristics and immune response in the airways are yet to be fully understood.

2. Discoveries of new pharmacotherapy for asthma are also awaited: we are in need of new targets with high specificity, low toxicity, convenient delivery and limited side-effects.

3. A better understanding of the immediate and long-term effects of existing combination asthma therapies, along with development of more efficient assessment, treatment and follow-up protocols, are among the clinical priorities.

4. We need better social support for the asthmatic children and their families in terms of safe housing conditions preventing/minimizing exposure to allergens, access to consistent and quality medical care, availability and adequate conditions for physical activity. Finally, education of all parties involved in care for asthmatic children requires expansion: we need dedicated and excellently-trained medical personnel at all levels, access for caregivers to relevant literature about the latest discoveries in areas of asthma research, diseases prevention and management, and last, but not least, we need a step-by-step action plan on how to educate affected children to efficiently deal with asthma on daily bases and yet have a productive and enjoyable life.

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