Chapter

Environmental and Occupational Factors; Contribution and Perspectives on Difficult to Treat Asthma

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Abstract

There are multiple well-recognized environmental factors that contribute to asthma exacerbation. Exposures to many of them will get unrecognized and most of the time will remain constant without knowing it is the causative agent. For an early identification of exposures and causative agents, a systematic approach needs to be taken in consideration by the encountering physician. Multiple questionnaires had been implementing and discussing organic and inorganic factors as well intrinsic and extrinsic factors. It is well-recognized that environmental exposures can cause worsening of asthma, other allergic conditions and even more severe pulmonary diseases. Asthma is a very prevalent disease with increased incidence nowadays. In the last decade, multiple new medications had been discovered for the treatment of moderate-to-severe persistent asthma, which most of them target the cellular component of the disease such as eosinophils and specific Immunoglobins. In the era of personalized medicine, environmental and occupational factors in asthma are key players that need to be recognized early in this patient population. In this chapter will go over model of effects, mechanism of action of these environmental factors, recognition, course of action and management of this patient population.

Keywords: environmental factors, occupational factors, exacerbation, allergens and irritants

1. Introduction

There are usually multiple risk factors that could exacerbate patients with asthma and other respiratory diseases. There are some risk factors that can be recognized

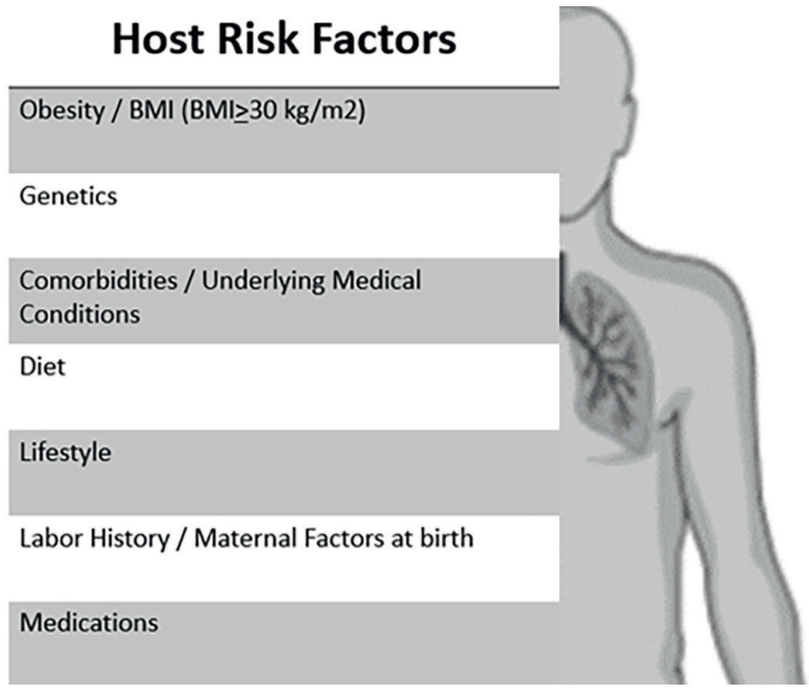

Figure 1.
Host factors contributing to asthma exacerbations.

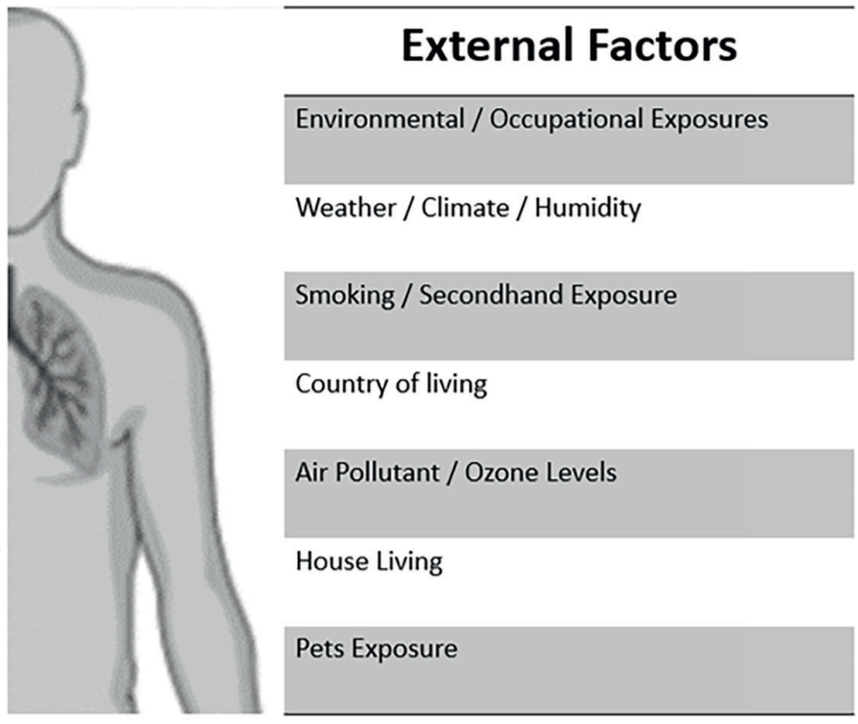

Figure 2.
External environmental and occupational factors.

quickly such as family history, smoking history and animals. There are Host factors contributing that contribute to asthma exacerbations (**Figure 1**), and external risk factors (**Figure 2**). further recognized other not so clear risk factors good understanding of asthma pathophysiology needs to be study. Asthma is a heterogeneous disease, characterized by airway hyperresponsiveness, chronic airway inflammation, reversible

airway obstruction and remodeling of the lung, leading to respiratory symptoms, which includes shortness of breath, wheezes, chest tightness and cough [1]. These symptoms vary over time in intensity and are present with variable expiratory airflow limitation [2]. However, airflow limitation may become persistent later in the course of the disease, making this condition difficult to treat [3]. Diagnosing asthma in the setting of multiple environmental factors is a challenging work, however at some point patients will lead the physician for specific factors that worsens the disease. Irritant's exposures will lead to asthma symptoms in specific situations which makes this heterogenous disease sometimes a predictable one [4]. Uncontrolled asthma is when patient has either poor symptom control (frequent symptoms or increased use of rescue therapy, when have limited activity due to asthma, night waking due to asthma or have frequent exacerbation, defined as more than 2 exacerbations a year requiring oral corticosteroids or serious exacerbations (> 1/year) requiring hospitalization [3]. Difficult to treat asthma is when there is poor symptom control, despite patient been on optimal therapy. Optimal therapy includes maintenance treatment with medium or high dose inhaled corticosteroids (ICS) or oral corticosteroids with a second controller, which is usually a long-acting beta agonist (LABA) or with maintenance of oral corticosteroids.

It is known that asthma is a multifactorial condition that includes a combination of genetic and environmental factors [5]. Early recognition is critical in the proper management of asthma, as well as to prevent exacerbations and complications [6].

Environmental factors induce airway inflammation that leads to an exaggerated hypersensitivity that cause airway obstruction [5]. This response is the result of an increased presence of eosinophils, lymphocytes, and mast cells leading to airway inflammation and damage to the bronchial epithelium. The most common cause is IgE-mediated type I allergen exposure response [7]. Environmental factors that contribute to asthma symptoms and severity include viral infection, allergens (cockroaches, dust mites, pollens, animal dander and molds), indoor and outdoor air pollution, tobacco smoke (passive and active smoker), occupational sensitizers (isocyanates, platinum salts, animal biological products), and other causes such as exercise food allergies, GERD, Aspirin or NSAID sensitivity, among others. Occupational asthma is an important part of the environmental factors that contribute to difficult to treat asthma. Occupational exposures are a major cause of lung disease and disability worldwide [8, 9]. It is estimated that work related exposures account for as much as 15–25% of the asthma burden in the United States [10]. Work-related asthma may cause functional impairment and disability and tends to cause higher morbidity than general asthma [11]. In new cases of asthma presentation in adults with an unknown trigger, work-related asthma should be considered.

1.1 Work-related asthma (WRA)

Early recognition of this entity and control of exposures are important in work-related induced asthma, because low-molecular-weight chemical sensitizers, also cause asthma in a similar mechanism of allergens [7]. WRA is divided into 2 categories: (1) Occupational asthma (OA), which is define as the asthma that is caused by exposition of an agent at work and (2) Work exacerbated asthma (WEA), with is defined as pre-existing asthma that is exacerbated by exposure to an agent at work. OA is suggested by a correlation between asthma symptoms and work, as well as with improvement when away from work for several days. It is cause by agents that are classified depending on their molecular weight; high-molecular-weight (HMW) or low molecular weight (LMW) agents [12]. The HMW antigens consist of animal and plant proteins, fungi, and other large organic molecules. The LMW antigens consist of chemicals and some metal salts [13].

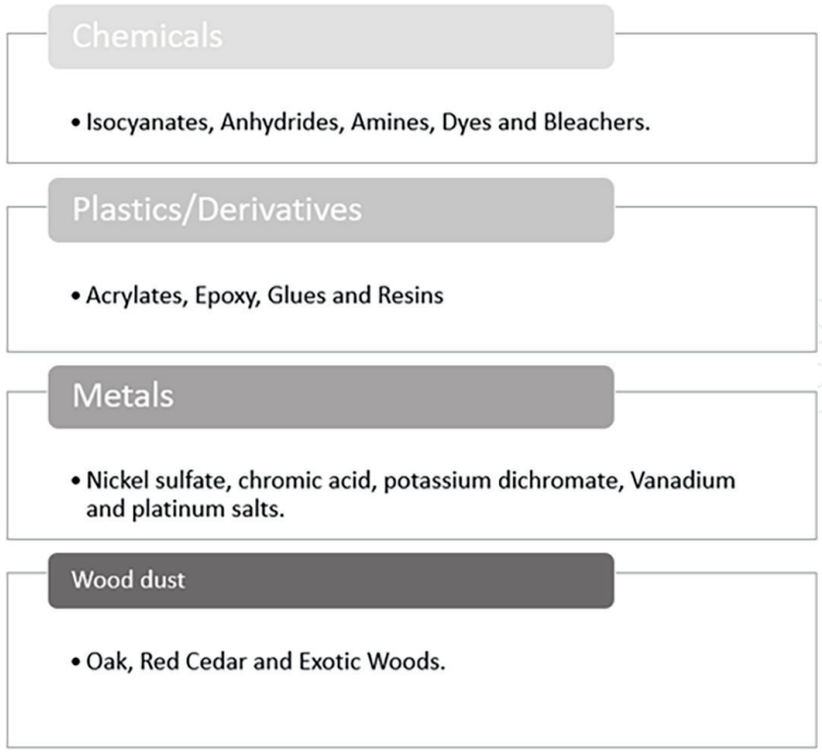

Figure 3.
Inorganic occupational exposures contributing to difficult to treat asthma.

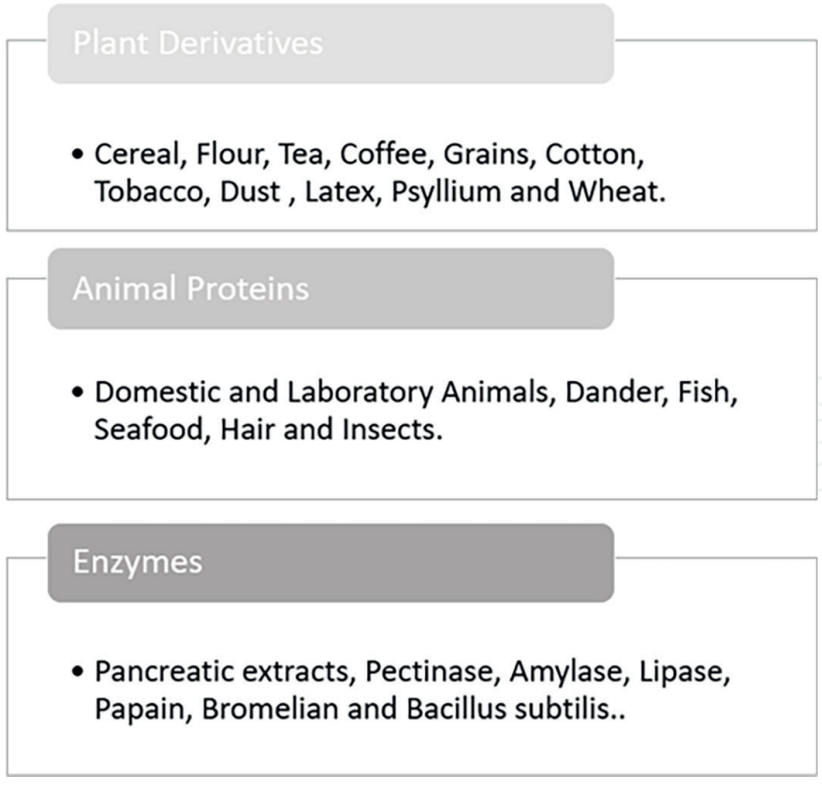

Figure 4.
Organic occupational exposures contributing to difficult to treat asthma.

It is thought that the LMW act through type I hypersensitivity mechanism, producing specific IgE antibodies, but the entire mechanisms are not well understood [12]. It is know that offending agents can cause an acute inflammatory response inducing reactive

Major Occupational Asthma Causes		
Offending agent	**Examples**	**Occupation/Environment at risk**
Low molecular weight irritant		
Drugs	• Beta-lactam antibiotics, opiates	Pharmaceutical workers, farm workers, health professionals
Chemical dust and vapors	• Isocyanates → Hexamethylene diisocyanate, toluene diisocyanate, diphenylmethane diisocyanate, naphthalene diisocyanate. • Anhydrides → Phthalic anhydride, trimellitic anhydride • Amines → Quaternary amines, chloramine. • Dyes and bleaches → Henna extract, anthraquinone, reactive dyes, carmine, persulfate.	Manufacturers of many industries such as upholstery, foam mattresses, insulation, polyurethane, plastics, paints and platers, welders, metal and chemical workers, packaging materials
Plastics and derivatives	• Acrylates, epoxy, other glues and resins	Plastic and resin manufacturers
Wood dust	• Oak, red cedar, exotic woods	Carpenters, woodworker
Metals	• Nickel sulfate, chromic acid, potassium dichromate, vanadium, platinum salts.	Welders, platers, metal and chemical workers
High molecular weight irritant		
Organic dust (Plant and Animal Substances)	• Plant derivatives → Cereals, flour, tea, coffee, grains, cotton, tobacco dust, latex, psyllium, wheat. • Animal Proteins → Domestic and laboratory animals, dander, fish, seafood, hair, small insects. • Enzymes → Pancreatic extracts, pectinase, amylase, lipase, papain, bromelain, *Bacillus subtilis*.	Farmers, cotton and textile workers, carpenters, woodworker, dusts from cotton and textile manufacture, veterinarians, dock workers, bakers, food processors, detergent manufacturers, health and pharmaceutical professionals, animal handlers

Figure 5.
*Major occupational asthma causes divided by molecular weight into low molecular weight irritant and high molecular weight irritant. **Rosenman KD, Beckett WS. Web based listing of agents associated with new onset work-related asthma. Respir med. 2015 may; 109(5):625–31.*

airways dysfunction syndrome, if exposure is repeated a chronic inflammation is produced that leads to persistent or permanent changes consistent with asthma [12]. It is important to recognize this offending agent as early as possible to prevent these changes. The most frequent causes of OA are Flour (31%) Isocyanates (17%), Persulfates (7%), Metals (4%), Wood (3%), Latex (3%), Acylates (3%), Quaternary ammonium (3.2%), Others (28%) [13], this factors can be divided into inorganic (**Figure 3**) and organic (**Figure 4**) risk factors, high molecular and low molecular weight (**Figure 5**).

**Torén K, Brisman J, Olin AC, Blanc PD. Asthma on the job: work-related factors in new onset-asthma and in exacerbations of pre-existing asthma. Respir Med. 2000 Jun;94(6):529–35.

2. Clinical assessment: physical examination and medical history

The signs and symptoms of asthma vary widely among every individual, as well as over time. This reversible airway obstruction pulmonary disease is characterized by the presence of several symptoms including nonproductive cough, chest tightness, episodic wheezing and dyspnea usually brought spontaneously or after exposures of

identified triggers or stimuli and relieved or improved with the use of bronchodilator therapy. Diagnosis is often difficult, as clinical presentation is nonspecific and my overlap with other comorbidities. The diagnosis of asthma involves a careful and detailed process of history taking, physical examination, laboratory studies and diagnostic studies which demonstrate variable expiratory airflow obstruction [14]. Asthma can affect any age, but is more common during childhood years, till many patients may have a remission of the disease during puberty with recurrence of the disease once day enter adulthood. Most cases of adult-onset asthma are usually related to occupational exposure, associated with aspirin induced or described as an eosinophilic type of asthma [15]. When evaluating a patient with suspected asthma; history taking should focus on aspects such as the presence of symptoms, the pattern and frequency of such symptoms, what are some precipitating factors and the existence of atopy, among other risk factors. There are some physical examination findings (**Figure 6**), which increase the likelihood of asthma and include the presence of nasal secretions, nasal swelling, and presence of nasal polyps, which are common in patients with allergic asthma. Cough may be dry or productive, where sputum have a pale yellowish discoloration which is secondary to presence of eosinophils and usually worsen at night. Chest tightness is most like band like, with feeling of heavy chest compression. Atopic dermatitis and eczemas are the most common skin manifestation noted in patients with asthma.

Chest examination may be normal between exacerbation, but during exacerbations there is limited airflow to cause wheezing, for which patients present with reduced breath sounds with prolonged expiration. Tripod position, use of accessory muscle of respiration and prolonged expiration (defined as decreased I: E ratio), are also noted during acute asthma exacerbations.

There are several risk factors that are involved in the development of asthma and many of them are an interaction between both host and environmental factors. Several studies have identified genetic factors that predispose to asthma, but these interact with other environmental factors such as indoor allergens such as furred

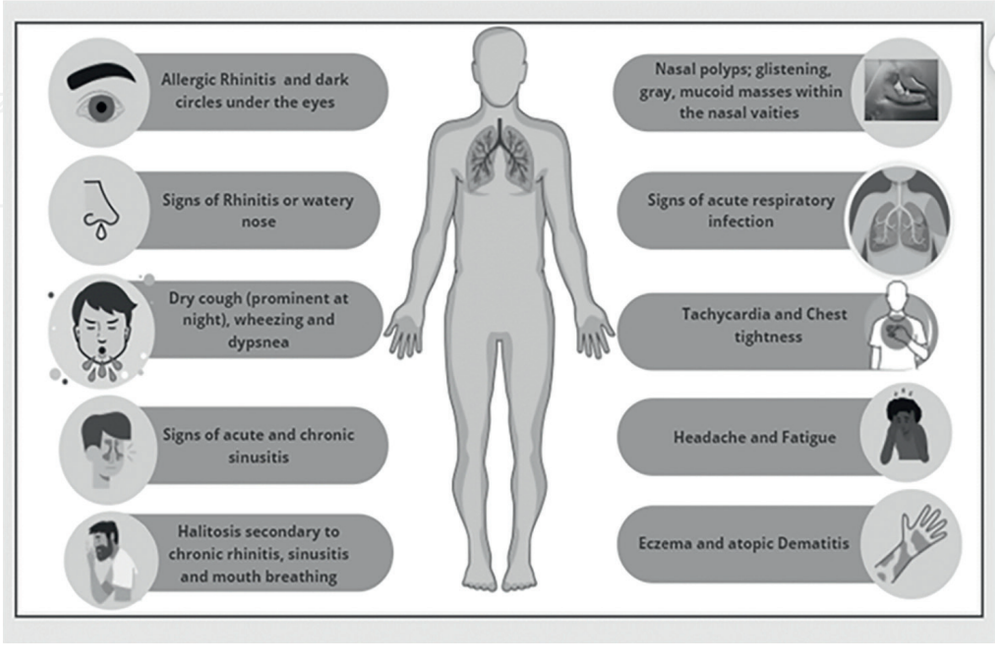

Figure 6.
Common clinical features in difficult to treat asthma that relates to environmental and occupational exposures.

animals, dusts, rodents, mold and cockroaches, as well as outdoor allergens as mols, pollen, air pollution, fumes, occupational exposure, and viral infections. History of tobacco smoking, second hand smoking exposure and commodities such as obesity, are also important risk factors. A personal history or family history of atopy may be present, characterized by seasonal allergies, atopic dermatitis and conjunctivitis, is common. There are cases, where patients have sensitivity to aspirin, presence of nasal polyps and wheezing, commonly known as the "asthmatic triad". This specific asthma symptoms, can be further recognized and attributed to specific situations were an environmental or occupation factors is present. When dealing with environmental exposures one of the most common symptoms that patients will be expressing is sneezing, rhinitis, and shortness of breath that can be divided in to dry cough or chest tightness, that most of the time will lead to increase in asthma regimens. Most of the patients will have some kind of relieve when they completely avoid this exposures such as vacation times or time off at home, however most of the environmental factors present at work place environmental can be found at home.

2.1 Diagnostic modalities

Establishing the diagnosis of asthma requires evaluation with a pulmonary function test (PFT). Other test such as laboratory testing, chest x-rays and allergy testing are mainly used to identify the different phenotypes of asthma. Arterial blood gas examination is also use and help to identify those patients with respiratory acidosis or increase CO2 that are in impending respiratory failure and may require mechanical ventilation as part of their treatment. In severe exacerbation, patients may present with hypoxemia and increase alveolar to arterial oxygen gradient, requiring oxygen supplementation. The PFT determines the degree and reversibility of airflow obstruction. Spirometry prior and after bronchodilation therapy is used for proper evaluation of the forced expiratory volume in one second (FEV1, forced vital capacity (FVC) and FEV1/FVC ratio. These measurements aid in the determination of airflow obstruction and reversibility of the disease. Airflow obstruction is defined as a ratio of FEV1 to FVC less than 0.70 or less than lower limit of normal. Severity of the disease is determined by the degree of reduction in the FEV1 below normal values. Patient with a FEV1 more than 70% predicted are classify as mild obstruction, a FEV1 between 50 to 69% predicted have moderate obstruction and FEV1 less than 50% predicted have severe obstruction [16]. Reversibility is determined by an increase of 12% or more than 200 ml in the FEV1 or FVC after the use of inhaled bronchodilators. Diagnostic modalities such as peak flow meters can be used when specific environmental factors are present and it will lead to variability of flow at this situations, and disappearance of this reduction in flows when not at contact.

In patients where spirometry is not diagnostic, a bronchial provocation testing with methacholine or histamine is used to diagnose asthma. A positive testing is defined as a reduction in the FEV1 of 20% or more or 8 mg/ml. When patient have a negative result there is 95% chance of ruling out asthma as the diagnosis, due to this testing high negative predictive value. Another important tool that is used to monitor or quantify asthma severity is the Peak Flow. This serves as an objective tool used by clinicians and patients, to monitor flow variability and response to medical treatment. Peak flow depends on patient's height, weight and age but these are poorly standardized markers and measurement tends to vary as the day goes by. It is recommended that peak flow be used early in the morning after the use of bronchodilator therapy and in the afternoon. Patients that have a change of 20% or more from morning

measurements or from day to day, suggest that patients have an uncontrolled asthma and required medication adjustments. If there is less than 200 L/min then there is severe airflow obstruction [16].

Imaging studies are not routinely done, as most patient have normal chest X ray. Some patients may show hyperinflation, diminished peripheral vasculature and bronchial thickening. Chest imaging are usually done when other superimpose conditions are suspected such as pneumonia or pneumothorax are suspected. Skin testing in combination with serum IgE leves is sometimes used together to better evaluate patients with atopy and aeroallergens, which in some cases will provide clinically relevant information. Absolute eosinophil count is requested for evaluation of eosinophilic asthma which benefit from anti IlL5 monotherapy. Finally, evaluation of the paranasal sinus and esophagus is done to rule out gastroesophageal reflux disease or paranasal sinus disease as a possible cause for refractory or persistent asthma.

3. Environmental and occupational triggers of asthma

The purpose of this section is to review indoor air pollution factors that contribute to asthma exacerbation, not controlled symptoms and difficult to treat disease. Its important to note that we spend most of the time in the indoor environment which makes this environment the most susceptible to this patient population, and most of the time very difficult to control. When we are dealing with a difficult to treat asthma patient, we need to have a good sense of the patient surroundings such as work, home and most visited places during the day. Analysis of time exposure with symptoms is important, to down-regulate possibilities and get to the causative factor. The steps to establishing causative and effect relationship between exposures is a complicated and essential component in management patients with strong environmental effects. Discussion will be made separating indoor with outdoor environmental factors, as well most recognized causative agents.

3.1 Indoor air pollution

There are many sources of indoor air pollution, which can be increase with outdoor pollutions contaminant. Exposure to indoor air pollutants can cause detrimental health issues, which could cause minor symptoms such as allergies represented with constant sneezing, coughing which can be exacerbated with indoor change in temperatures and irritants [17]. This irritant could cause only upper respiratory symptoms; however, it could get complicated with lower respiratory symptoms such as reactive airway disease and bronchial asthma exacerbations in patients with underlying hyperactive airways. It's important to note that indoor environments will get outdoor mixtures of pollutants in which will reaccumulate with indoor sources causing a conjoined effect. Indoor factors could range from animal matters, molds from humid areas, secondhand tobacco exposure and dust mites among others that will be further discuss.

3.2 Particulate matter

It consists of particles suspended in the air which can be from human sources such as factories, vehicles, personal or community transports, electricity plants and industrial fumes, or natural matters such as pollen, spontaneous fires, spores, animal debris and

plants among others. It's important to note that particulate matter can be divided with sizes going from particles less than 10 um in diameter (PM10) to particles less than 2.5 um (PM2.5) [18]. One of the strongest clinical differences between this particle is that particles less than 10 um could enter the respiratory system, and the smallest ones will be able to enter the alveoli which is the distal component of the airway. Particles that are between 2.5 um to 10 um will not be able to reach the alveoli but will be possible to deposit in the more proximal airways in which the clinical sequela will be different. With this it's important to point out that proximal airway deposition will have a clinical presentation of asthma, with reactive airway disease, which may cause inflammation and subsequent exacerbation of underlying asthma. Multiple studies have shown that strong particulate exposure led to lower pulmonary function and deterioration overtime [19]. Physiology of particulate matter starts when it enters the body through the nose and mouth when we are breathing, at that moment the body will be able to eliminate most of the largest particles which are the ones more than 2.5 um, but the other smaller particles will continue passage into the lungs and have detrimental stationary inflammatory effects in the alveoli. This effect could lead to interstitial lung disease with permanent parenchyma damage as well acute diseases such as hypersensitivity pneumonitis, chronic bronchitis among others [20]. It will not only lead to respiratory symptoms if can case cardiovascular complications such as arrhythmia and coronary artery disease. This makes particulate matter a detrimental environmental factor to the healthy people but most importantly to patients with comorbidities such as asthma.

3.3 Indoor nitrogen dioxide

Nitrogen dioxide is an irritant gas that has strongly been linked with respiratory symptoms with negative long term sequelas. It's a product of elevated temperature combustion as can been seen in indoor gasses such as indoor stoves. There are other sources of NO2 such as power plants which is specifically important in low-income countries with poor power supply, as well diesel power construction machines and industrial machines. It's important to note that even though most of the NO2 sources are from the outdoors, this outdoors contaminants could penetrate inside houses and became constant irritants to the households, making patients with pulmonary diseases more vulnerable [21]. Severe health effects of NO2 exposures would affect proximal airway causing worsened of cough with wheezes, causing increased in asthma exacerbations, leading to more hospital admissions. Constant exposure will eventually cause increased airway inflammation with remodeling of the airway, making it more severe with time. This patient will be escalating asthma treatments quickly without major relief and eventually will ne on advanced asthma treatments of this exposures are not recognized. There are multiple scientific studies that link decreased in pulmonary function such as diminished peak flows with higher exposure of N02. Avoidance and early recognition of improperly used heating devices and combustion devices is of greatest importance for avoidance [22]. Special attention to poorly vented placed, in which combustion products are been produced such as Nitrogen dioxide (NO2), carbon monoxide, Sulfur dioxide (SO2) and particulate matter as previously mentioned is key on the management of this patients.

3.4 Dust mites

Dust Mites are a worldwide problem in respiratory vulnerable patients. This are tiny organism that live in furniture's such as beddings, bed, soft toys, and clothing

most of the time at people's homes. This organism is not airborne they live in soft and humid environments [23]. Dust mites most of the time become airborne with cleaning activities such as vacuum and dusting which organism will be mobilized and as other particulate matter react to nasal receptors and start the perpetuating sequela. Dust mite allergies can be detected with blood samples, for better preventive measures which the goal when recognizing exacerbating factors. Other preventive measures that will be discussed is the use of allergen proof mattress with pillowcases, close washing of bedding in a weakly basis, carpets and rugs management with high efficiency particulate air filter. The physiology of symptoms starts with indoor mites that are constantly feeding from death skin, that eventually will liberate allergens during that chemical process that will eventually lead to an asthma trigger, that most of the time will start with upper airway symptoms, with eventual bronchospasm due to airway hyperresponsiveness. It's important to recognize Dust mites because it's a strong allergen, difficult to take care of, and take meticulous weekly indoor management protocols for prevention of exacerbations. Asthma medications can help ameliorate dust mite reaction, but preventive measures with bedding cleaning, keeping beds with dust proof covers as well warm cleaning with higher degree temperature is the recommended range for adequate cleaning [24].

3.5 Cockroaches

Cockroaches are a worldwide populates pest with more than 3500 species known. They are most found in cities with highest urban population. Exposure to this indoor and outdoor pest, are well known causative agents of asthma and atopy respectively, and constant exposure this have been linked to increase asthma morbidity, which makes this environmental factors highly important in the recognition and management [25]. The cause of allergy and asthma exacerbations is been cause by proteins produced by cockroaches in which can be found in feces and body fluids of this animals. It's been stipulated that almost 60% of homes in the US have cockroaches, which is a big number comparing the high incidence of asthma and allergy, so we are continuously dealing with a difficult pest every day. There are several known cockroaches' species which are Blattella germanica and Periplaneta americana, which both produce the protein responsible for asthma triggers. Several proteins been recognized are Bla g 2(inactive aspartic proteinase), Bla g 4 (calycin) and Bla g 5 (glutathione-S-transferase) [26]. With these molecular recognized proteins, we can quantify exposure levels, which will eventually help in difficult to treat patient with asthma, in which exposure or triggers have not been recognized and subsequently avoided. Cockroaches induced allergic inflammation is the main driver in asthma exacerbations and difficult to manage asthma patients, this excreted particles from this organism can gain access to the upper respiratory tract through the nose and oral cavities with dislodgment into the lungs causing allergen epithelial damage. Cockroach allergy is diagnosed with crude extract via skin testing or direct measurement of serum specific IgE to this specific allergen, in this case cockroach. This serum levels can be use to recognized other multiple specific allergens. However, even though good sanitation and successful extermination actions are taken, sustained decrease in allergens levels is difficult to accomplish. It's important to recognized other environmental factors in this patient such as constant particulate matter exposure because air pollutants can increase the allergic effect of cockroaches and other indoor allergens with a synergistic relationship, a multidisciplinary approach for recognition is recommended to be effective in management.

3.6 Cats

There is a strong association between pet ownership and new onset asthma as well the development of allergic symptoms. Cats had been recognized as a major source of allergens for many years. They can produce numerous allergens that can trigger asthma symptoms. These allergens can be found in cats saliva, in which at the act of cats self-grooming its transfer to the skin, producing contact dermatitis changes as well can be inhaled in combination with cats dander causing asthma as well causes difficult to treat disease in patients with continuous exposure. Cats dander is another component of cats that comes from dead skin sweat glands that can suspend in the air consequently getting into the airways. As can be seen in other animal allergic sources component, cats urine can be the source of asthma, ligated with the protein Felis domesticus (Fel d 1) found in urine which can cause airway diseases as well [27]. Touching or inhaling these allergens causes overreaction of the immune system, leading to worsening of asthma symptoms. Asthma in adults differs from children in which atopy and exposure to aeroallergens are a determinant factor that could cause airway hyperresponsiveness [28]. Allergic asthma is a difficult to treat disease, however blood markers with specific IgE components which can be range from rFel d 1 which is a marker for severe asthma, and specifically indicates that is related to cats. Other components been found in asthma is rFel d 2, rFel d 4 and r Fel d7 by which its less specific for cats because it can be present in patients with dogs, horse and mice exposures [29, 30]. The best therapeutic option in this patient population is to avoid contact with animals specially cats or dogs, and very importantly to avoid indirect contact with areas that animals spent time. Keeping animals in the outdoor setting is appropriate, however allergens will remain in indoor spaces, by which aggressive hygiene needs to take part on the management.

3.7 Molds

Mold is a fungal growth that spread in surfaces, where most of the will be organic matter however it's not always the case. It can be found indoors and outdoors respectively, they will most of the time look for excess moisture places which is the most common cause of indoor mold environment. Molds are well recognized allergens related to asthma exacerbations, and most of the time will go not recognized [31]. Inhaling or contact with molds can cause allergic reactions, in which can trigger asthma symptoms, which can be manifested as sneezing, throat irritation, nasal stuffiness with runny nose and watery eyes, which are active signs of ongoing allergic process. Most of the patients will recognized this early symptom and could be able to attach specific interaction with the causing allergen, however molds are more difficult to be recognized. Most of the sources of mold in indoor settings will have water leaks associated with it, such as can be seen in air conditioners and leaks from outsource of water in close buildings. Molds not only can exacerbate asthma, but they are also well recognized factor of causing fatal respiratory conditions such as hypersensitivity pneumonitis which can be acute and could lead to respiratory failure [32]. There are several home situations even outdoors that needs to take in consideration when dealing with molds, and it's the existence of plumbing leaks, roof leaks and high humidity places, mostly indoors. Management of high-risk exposure places is important in occupational environmental, by which early detection in the setting of high suspiciousness is of great importance. Regular inspection of buildings, regular schedule air conditioning cleaning, adequate ventilation of close spaces and the importance of developing a indoor environment quality

control group that will remain on top of this circumstances for adequate management [33]. Molds can produce spores which can be inhaled, that will produce allergic symptoms with upper airway predominance, this mold could weaken the natural defense mechanism o the airway that could lead to predisposition to colds and flu diseases. Special interest is been taken about molds in occupation setting environments, in which working personnel will became symptomatic in specific working areas and not at home places, in this special setting aggressive interrogation and evaluation is of most importance to prevent future exacerbations of lung diseases specially asthma.

3.8 Pollens

Pollen is the composition of tiny grains produced by plants for the purpose of fertilization. The wind is the main driver to spread the pollen to different areas, remaining most of the time suspended in the air. It is an important asthma allergen which could exacerbated allergic symptoms such as conjunctivitis, rhinitis and respiratory conditions [34]. Polinization periods are recognized as the peaks in pollen grains in the environment which remain suspended in the air causing allergic symptoms at inhalation. It had been recognized that pollen can be simultaneously combined with air pollution, increasing the changes of asthma and makes particles more easily to breath in. This makes polinization seasons challenging to physicians, making difficult to treat patients most vulnerable to this factor. Pollen season ranges from March to April respectively in which it can last up to 6 months [35]. There are multiple algorithmic maps which shows the percentage of pollen counts around the United States in which it can be characterize as low (0–2.4), low medium (2.5–4.8), medium (4.9–7.2), medium high (7.3–9.6) and high (9.7–12). It's important to understand that dry, windy days can cause allergy symptoms to get worse, however humid and rainy days can sometimes be beneficial to people with allergies. Physiology of this correlates making heavier pollen molecules making it most likely to stay on the ground.

3.9 Environmental tobacco smoke (ETS)

Environmental tobacco smoke is generated by the combustion of tobacco smoke. It is commonly emitted with combustion, which is actively exhale from the smoker. Tobacco smoke is composed of more than 4000 toxic compounds, most of them well known to have carcinogen effects [36]. There are two types of environmental tobacco smoke, which can be divided into side stream smoke which is the smoke from tobacco that is released from the end of a burning cigarette or tobacco pipe. Mainstream smoke refers to the smoke that is inhaled by a smoker that is actively exhaled to the environment and subsequently inhaled by a second person causing inhalation exposure. Side stream smoke is also of danger if prolonged exposure of time, side stream can persist affecting the smoker and not smoker in close rooms [37]. Several factors had been recognized that can affect the amount of side stream smoke which is humidity, temperature, open ventilation versus close ventilation and number of active smokers in the room. At this moment there is some data suggesting that second hand smoking can cause obstructive lung diseases as well however it's something that under investigation.

3.10 Outdoor air pollution

There are several groups of air pollutants which are ozone, particulate matter as previously discussed, sulfur dioxide, nitrogen dioxide, carbon monoxide and lead

Environmental Triggers of Asthma			
Mold and moisture	Environmental Tobacco Smoker	Gas Stoves	Viral Infections
Dust Mites	Hairspray/Personal Chemical Irritants	Wood Smoke	Sinus Inflammation
Cockroaches and Rodents	Air Conditioning	Outdoor Pollution/Particulate Matter	Emotions
Strong Odors/Perfumes	Food/Drinks	Nitrogen Dioxide/Sulfur Dioxide	Exercise
Weather/Cold Air	Grass	Molds	Medications
Animal Exposures	Cleaning Products	Workplace Exposure	Ozone
Pollen	Pesticides	Humidity	

Figure 7.
Environmental triggers of asthma.

respectively. There are multiple environmental triggers of asthma (**Figure 7**). Its Ozone the most recognized factor linked to asthma exacerbations, as well the cause of triggering asthma symptoms. Ozone forms in the air it's not visible, it cannot be smell or taste neither, but it can have strong health impact aggravating asthma symptoms, subsequently increasing use of medications, as well admissions to the hospital due to respiratory conditions. Ozone can be worse in patients with asthma, by which they will be more responsive to inflammation [38]. There are several studies comparing ambient ozone concentrations with increased asthma symptoms, as well risk of hospitalizations and decompensation. There is a positive correlation between severity of asthma and risk of ozone related effects. Traffic related pollutants are part of outdoor environmental factors as well diesel exhaust combustions.

4. Treatment, management and prevention

As we mentioned before, asthma is a common chronic disease characterized by episodic or persistent respiratory symptoms and airflow limitation, requiring ongoing and comprehensive treatment with the goal to reduce symptoms and minimize the risk of developments of exacerbations, and treatment side effects. The pathophysiology of the disease is complex and heterogeneous for which treatment is based on a stepwise approach and the management is control-based. This involves interactive cycle assessment where symptoms and risk factors are evaluated, adjustment of treatment and review of response in which patient preferences should also be taken into account. Anti-inflammatory treatment has been the mainstay of asthma management to reduce airway inflammation and help prevent symptoms; among these are the inhaled corticosteroids. For rapid relief of symptoms short-acting beta agonists (SABA) are the ones used to reduce airway bronchoconstriction causing relaxation of airway smooth muscles. The National and International guidelines have recommended SABA as the first line treatment for patients with mild asthma, since the Global Initiative for Asthma guideline (GINA) was first published in 1995, adopting

the approach to control symptoms rather than the underlying condition. GINA was established by the WHO and NHLBI in 1993 to increase awareness about asthma and to improve asthma prevention and management through a coordinated worldwide effort. The SABA approach was initially thought to be due believing that asthma symptoms were related to bronchoconstriction rather than presence of a concomitant condition caused by airway inflammation.

GINA 2019 guideline review introduced substantial changes, adjusting asthma treatment for individual patients and adopting the concept of anti-inflammatory reliever in all degrees of severity as a crucial component in the management of the disease and efficacy of the treatment. The use of reliever medication (SABA) was placed as an addendum in the recommendations to be used in case the real treatment (the controller) failed to maintain disease control. As we know, SABA can effectively induce rapid symptom relief but are ineffective on the underlying inflammatory process. To achieve control, the intensity of the controller therapy was related to the disease severity with preferred controlled choice varying from low-dose inhaled corticosteroids (ICS)/long-acting bronchodilator (LABA), medium-dose ICS/LABA, up to high-dose ICS/LABA and with a SABA as the rescue medication. As a result of this patients with mild disease or mild symptoms were left without any anti-inflammatory treatment such as ICS and relying only on SABA rescue treatment. An important point to mention is one of the major limitations for control of asthma, which is poor adherence to therapy. A lot of patients seem to be administering inhaled medication only when asthma symptoms occur. In the absence of symptoms, patients perceive therapy unnecessary and avoid taking controlled medication. Therefore, when symptoms worsen, patients prefer to use reliever therapy which could result in overuse of SABA. An as seen in previous studies, there is evidence that suggest that overuse of beta-agonist alone is associated with risk of death from asthma, and at the same time with each exacerbation the risk of death also increases. Regular use of SABA, even for 1–2 weeks, is associated in increased airway hyper-responsiveness (AHR), reduced bronchodilator effect, increased allergic response and eosinophils [39].

Based on this evidence, in latest GINA 2022 guidelines treatment options are recommended in 5 Steps and divided in two tracks, to clarify how to step treatment up and down with the same reliever. First track which is the preferred strategy, is with the use of low-dose ICS/LABA (formoterol) as a reliever, introducing the single maintenance and reliever treatment (SMART). This strategy is the preferred due to evidence suggesting reduced risk of exacerbations compared with use of SABA only as a reliever, with similar symptoms control and lung function [40]. The SMART strategy containing the rapid-acting formoterol was recommended throughout GINA Steps based on solid evidence [41]. This recommendation continues since GINA 2019, where SABA as a reliever alone in STEP 1 was no longer recommended based on key studies SYGMA 1, SYGMA 2, Novel START and PRACTICAL [42, 43].

The second track, which is an alternative non-preferred strategy, is with the use of SABA as the reliever. This strategy is less effective in reducing exacerbations, however, continues to be used in case that therapy with low-dose ICS/LABA (Formoterol) is not possible. Also, it can be considered if patient has good adherence with their controller and has had no exacerbation in the last year. For patients who have asthma that remains uncontrolled after step 4 treatment should be referred for phenotypic assessment with or without add-on therapy. As mentioned before asthma is a complex and heterogeneous disease for which therapy should be individualized based on the underlying condition, presence or absence of allergy, and other coexisting conditions. In severe asthma or difficult-to-treat asthma, poor control can be linked to poor

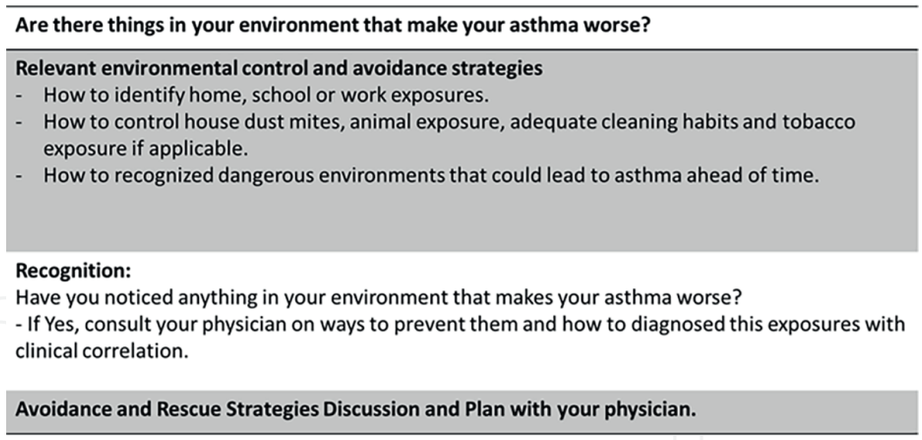

Figure 8.
Relevant questions to identify environmental factors contributing to difficult to treat asthma.

adherence to medication, incorrect inhaler technique, and coexisting conditions, including exposure to allergens and irritants. Based on this the National Asthma Education Prevention Program (NAEPP) they recommended multicomponent allergen mitigation in sensitized individuals who have exposure to indoor allergen for pets. It was recommended to do integrated pest management alone, or as part of multi-core component intervention, and for dust mites that recommended using impermeable covers only as part of multicomponent intervention. Immunotherapy is recommended in mild to moderate allergic asthma but recommended using sub cutaneous immunotherapy. Also, important component of this therapy is to avoid any allergens or irritants that may trigger disease including smoke, dust mite, cockroach, animals, etc. Irritant or allergen sensitivity can also be determined by patient exposure and symptoms history, confirmed with skin or blood test. Leukotriene modifiers who have been used widely are mostly used especially in aspirin exacerbated respiratory disease and exercise-induced bronchial constriction who have been shown to have greater response.

When we are dealing with environmental and occupation factors, we need to categorize the patient and start the adequate therapy. The most important step is to make the diagnosis which can be made with peak flow changes in different environments of interest or investigated exposures. Changes in symptoms with changes in expiratory flow are classic in environmental exposures causing symptoms. Most of the patients will have recognized symptoms when exposed to the irritant or allergen. In patients that exposure is not clear, several algorithms of identification can be used with specific questions of daily life activities. Relevant questions to identify environmental factors (**Figure 8**).

5. Conclusion

As been discussed during this chapter, there are multiple environmental and occupation factors that are well known to cause asthma and worsening of asthma symptoms. Many triggers been recognized that can be divided into allergic and non allergic which is important at the moment of symptoms interrogation. A methodology approach and personalized approach need to be done for early and proper recognition of this factors. Educational programs on avoidance and recognition needs to be provided to the general population as well, education regarding common symptoms

when dealing with this exposure which will eventually lead for better patient respiratory control and quality of life.

Conflict of interest

The authors declare no conflict of interest.

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