INTRODUCTION

Asthma is a bronchial disease which is characterised by chronic inflammation and which appears in tandem with dyspnoea episodes. It reduces quality of life of asthma patients by decreasing respiratory capacity, leading to intermittent or persistent bronchial obstruction. As such, asthma treatment focuses on controlling the disease. Asthma management and control are tightly bound up with patient's symptoms and the degree of obstruction and/or functional limitation to the respiratory airflow and volume.

ASTHMA EVOLUTION

Asthma evolution does not follow one single line; there are acknowledged different growth patterns and different asthma phenotypes with different components, symptoms and bronchial hyperreactivity manifesting in young children, through to childhood, adolescence and adulthood.

While the ideal asthma treatment is one which makes the patient asymptomatic and able to lead a normal life, in the majority of full-blown asthma cases or in moderate or severe asthma, the aim is to reduce the amount of hospital stay, attacks and nocturnal symptoms as much and as markedly as possible, in addition to improving the sufferer's quality of life.
In asthma treatment, knowledge of and intervention in possible associated conditions, respiratory or otherwise, is important, as treatment and control of these associated pathologies may be necessary. Rhinitis is a pathology frequently associated to asthma, particularly allergic asthma and rhinitis. Untreated or poorly treated allergic rhinitis is harmful to a patient with concomitant allergic aetiology asthma.

Treatment of acid reflux is vital in asthma patients with gastro-esophageal reflux as its presence and persistence worsens asthma symptoms and triggers attacks, which are sometimes hard to manage.

**PREVENTIVE PLAN**

An adequate prevent plan is vital in the treatment of both allergic and non-allergic asthma to cut risk factors. In cases of allergy to animals, avoiding exposure is paramount. In cases of house-dust-mite allergy, cleaning and ventilating the home is crucial and reducing exposure to the pollens, which trigger the pollen allergy, will diminish symptoms.

Other risk factors for asthma sufferers include upper or lower airway respiratory infections, physical exertion, cold, indoor (for instance, passive smoking) and outdoor pollution.

The asthma patient's emotional instability can give rise to decompensation and consequent asthma attacks.

International specialists have drawn up consensus guidelines for asthma treatment over the last ten years.

While their approach to treatment has been based on the severity of the symptoms and lung function capacity, particularly FEV1 and PEF, their practical application has not proved easy or consensual.

This is true of approaches to any chronic and inflammatory disease, such as asthma. Each patient has unique characteristics, making each case a
A personal approach encompassing comprehension of the disease and compliance with a suitable treatment schedule is needed. The doctor-patient relationship is also one of the main factors for successful control of the disease.

Asthma is an insidious, slow growth disease once it onsets, which usually occurs in childhood. It worsens over time through outbreaks of wheezing which are usually accompanied by cough. Two groups of medicines treat it pharmacologically.

Efficacious asthma treatment or control of asthma depends on several factors, including lung function, exacerbation rates, severity of exacerbations, symptoms scores, quality of life measurements and the impact of treatment on the underlying disease process.

MEDICATION

Medication to treat asthma can be divided into controllers and relievers.

Controllers are medications taken daily on a long-term basis.

This group includes inhaled and systemic corticosteroids, cromones (nedocromil and cromoglycate), leukotriene modifiers, sustained-release theophyllines and anti-IgE. Inhaled corticosteroids are the most effective controller medications currently available. Long-acting inhaled ß2-agonists (LABA) have appeared over the last decade and are currently used in association with ICS as controllers.

The second group integrates medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms. They included rapid-acting inhaled ß2-agonists, inhaled anticholinergics, short-acting theophyllines and short-acting oral ß2-agonists.

The ones most used worldwide are rapid-acting inhaled ß2-agonists.

The appearance of inhaled corticosteroids heralded a decrease in asthma mortality in developed countries, despite the increase in morbidity.
This pharmacological group is associated to a marked reduction in hospital stay, asthma attacks and use of reliever medicine. Regular ICS use in persistent asthma has been associated to an improved natural course of the disease with lessened symptoms, improved lung function in children and adolescents and a reduced pathology evolution via remodelling.

**CONTROLLERS**

The best route of administration of controller’s medications should be the inhaled. However, other route can be applied such as oral or parenteral (IM, SC or IV).

The inhaled therapy as the advantage to deliver the drug directly into the airways. Pressurized metered-dose inhalers (pMDI), now with the medication as a solution in hydrofluoroalkanes (HFAs) are the most used devices. Patients with asthma of any severity, including during exacerbations, could use these devices.

Some patients feels more advantage to manage dry powder inhalers, but with these devices require an inspiration with a minimal respiratory flow rate, which on elderly can be difficult to performed it.

Medications delivered by aerosol are an alternative for a patient who has difficulty to manage pMDI.

A good reviewed on a meta-analysis of randomized and controlled clinical trails comparing the efficacy and adverse effects of the delivery of beta-agonists, anticholinergics, or inhaled steroids by:

1) power nebulisation;

2) pressurized MDI (pMDI) with/without a spacer/holding chamber or

3) a dry powder inhaler (DPI), found no significant difference in the efficacy outcome in any patient group for each of the clinical settings that was investigated, provided that the correct technique was used for the devices studied.
It is very important that asthmatic patients should use a particular inhalation device correctly, because is more important than the type of the device used. However, in very young children who cannot manoeuvre a pMDI or a DPI, delivery by a nebuliser may be necessary.

The goal of asthma therapy is to reduce the burden of disease as experienced by the patient in terms of clinical endpoints, such as symptomatic relief (dyspnoea, awakenings, exacerbations or crisis), improved lung function, fewer days missing from work or school, reduced emergency room visits and hospitalization.

Every patient with persistent asthma should take knowledge that this is a disease with a real possibility of death.

Besides asthma symptoms, which can be measured by daily use of a symptoms card to registry them, biomarkers like lung function such as peak flow and FEV1, assays of hyperresponsiveness to exogenous stimuli (eg, methacholine, histamine, or manitol), eosinophils count in sputum and increased levels of fraction of exhaled nitric oxide.

On patient with intermittent asthma, there is a no-persistent asthma, and then with few symptoms along the year, usually, reliever medication is the standard.

Rapid-acting inhaled β2 agonists are the choice for relief of bronchospam during acute exacerbation of asthma and for pre-treatment of exercise-induced bronchoconstriction.

**RELIEVERS**

They include salbutamol, terbutaline, reproterol and pirbuterol.

They are quickly to relieve bronchoconstriction and its accompanying acute symptoms.

As note, formoterol a long-acting β2-agonist can be used for symptoms relief because of its rapid onset of action, but it should only be used for this purpose on regular controller therapy with inhaled steroids.
Rapid-acting inhaled β2-agonists should be used only on an as needed basis, at lowest dose and frequency required. This type of medication is always the first choice to treat acute asthma exacerbation in all grade of asthma severity, in either adults or children.

**MILD ASTHMA**

The best choice to treat mild asthma is ICS, which alone is sufficient to control the disease.

However, the ICS dose could be increase to reach a good control of symptoms or turn the patient asymptomatic.

The equivalence and dosage of ICS for adults (*Figure 1*) or for children (*Figure 2*) is useful to manage this type of medication on asthma patients.

*Figure 1. - Estimated Equipotent Daily Doses of Inhaled Corticosteroids for Adults*]

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*adapted from GINA Guidelines*
As alternative treatment on mild persistent asthma, we can use leukotriene modifiers (montelukast, pranlukast and zafirlukast) as controller, because they have a small bronchodilator effect, reduce symptoms including cough, improve lung function and reduce airways inflammation and asthma exacerbation.

However, leukotriene modifiers effect, when they are used alone, is low that low doses of ICS. Nevertheless, leukotriene modifiers can be used to reduce the dose of ICS required by patients with moderate or severe asthma.

Also, we know, that mild asthma treated with ICS with continued therapy was clearly superior to a switch to LABA administration alone. Several studies have demonstrated that asthmatic patients can be at risk for adverse clinical outcomes after discontinuation of ICS.

On mild asthma therapy, cromones can be used, alone or added to ICS or LABA, however such medication are, actually, not recommended due to small anti-inflammatory effect and long-term on asthma treatment is limited. Their efficacy has been reported in children and adults with mild persistent asthma, however the efficacy compared with ICS is very low.

**MODERATE ASTHMA**

When patients have moderate persistent asthma ICS is still the first choice, with medium or high daily dose, however add LABA to medium dose of ICS could be a good alternative to reduce some side effects of high dose of ICS. In last years, the association of ICS with LABA in a same device is a very good choice to reach the asthma control in this group of patients, and this combination therapy is preferred treatment when a medium dose of ICS alone fails to achieve control of asthma.

Asthma patients under ICS continued therapy had significantly less subsequent asthma related hospitalizations or emergency treatment visits then those in whom controller medications were less than 50% of total asthma medication use.
Leukotriene modifiers and/or theophylline medication can be added to ICS+LABA association as add-on therapy in patients who do not achieve control of symptoms.

The aim is to control asthma symptoms, so leukotriene modifiers can be added during a period from 3 to 6 months and the issue is well controlled, the treatment must continue for a long-period. Otherwise, theophylline can be added to ICS+LAVA to reach asthma symptoms control.

When both alternatives fail, higher dose of ICS should be performed. In these patients, the management of ICS and LABA association administration can be done on different devices to reach our objective, which is always asthma symptoms control and promote a better quality of live on asthmatics.

When to control asthma symptoms, inhaled corticosteroids in high dose added long-acting β2-agonists, is needed and associated with leukotriene modifiers and/or theophylline, is not sufficient to have a good control of asthma, we, without any doubt, are in a presence of a severe asthma patient.

Although many asthma cases can be controlled with a combination of anti-inflammatory drugs as steroids and bronchodilators, there are patients who remains symptomatic despite combination of several medication.

These patients represent a heterogeneous group consisting of those who are under-treated or non-adherent with their prescribed medication. After excluding under-treatment and poor compliance, corticosteroid refractory therapy asthma can be identified as a sub phenotype characterised by a heightened neutrophilic airway inflammatory response with evidence of increased tissue injury and remodelling.

SEVERE ASTHMA

On a severe persistent asthma patient, we should look to other pathologies with interaction with asthma is recognized, such as GERD, sinusitis, nasal
polypus, hormonal disturbance, etc. In addition, we such remind that the pathogenesis of asthma is likely quite complex.

When a patient has a severe persistent asthma to control symptoms, the association of higher dose of ICS, LABA, leukotriene modifiers and/or theophyllines should be used on first approach. Whether asthma symptoms control could not be reached, oral corticosteroids must be associated.

The goal is control the symptoms and asthma exacerbations, so the dose of oral corticosteroids should be started from 40-60 mg daily of prednisone, on adults, to achieve the control of the disease for a period of 3-4 weeks.

When uncontrolled asthma is turned to a controlled asthma oral corticosteroids decrease can be made.

Therefore, as measure as possible, a dose of 5 mg every week to reach 5-10 mg daily or even stop this medication when asthma symptoms control is achieved. On failure to control symptoms hospitalization is strongly recommend.

We must be aware that to reach asthma control, regular clinical observations are needed as well as asthma outcomes should be evaluated monthly on severe asthma patients.

After asthma symptoms, control is achieved trimester clinical evaluation could be performed.

Asthma symptoms severity, asthma scores and quality of life are significantly more favourable in asthmatics patients in whom asthma controller medications were at least 50% of the total asthma medications.

For patients with mild asthma who are unable to use inhaled medication, as alternative we can use leukotriene modifiers alone or associated with oral sustained-release theophyllines for short periods. On patients with moderate asthma leukotriene modifiers associated with oral sustained-release theophyllines and short-acting oral β2-agonists, could be done, however side effects should continuous be evaluated.
ASTHMA IN CHILDREN

Asthma treatment in children is quite similar to adult asthma treatment, however route of administration and drugs dose are quite different31

Inhaled therapy is the first choice for children of all ages, however different age groups require different inhalers, so the choice of the inhaler should be individualised. In general, a metered dose inhaler (pMDI) with spacer is preferable to nebulised therapy due to is greater convenience, more effective lung deposition, lower risk of side effects and lower cost.

Nebulisers due to imprecise dosing, time consuming to use and to care, required maintenance should be reserved for children who cannot use other inhalers devices.

On children under 4 years old, pMDI plus a dedicated spacer with face mask is recommended. There are several types of facemask according to age from newborn to 4 years old.

For children aged from 4 to 6 years old a pMDI with a spacer and a mouthpiece is appropriated to treat asthma symptoms. For children older than 6 years dry powder inhalers or pMDI with spacer or mouthpiece is recommended.

Both relief medication (rapid-acting β2-agonist or anticholinergics) and controller medication (ICS and long-acting β2-agonist), can be performed by these devices (pMDI e dry powder). Many children older than 4 years can manage a dry powder inhaler without difficult, which is good to carry them to school.

On mild and moderate asthma in younger children, ICS or cromones can be used, however ICS inhalation suspension was more effective that nebulised cromolyn sodium and was well tolerated in young children with moderate asthma symptoms.
There is a general agreement that ICS of persistent asthma in young wheezing children leads to a decreased asthmatic symptoms, use of rescue medications, and less frequent acute asthma exacerbations.

However, other factors (e.g. local smooth muscle hyperactivity) may persist despite chronic low or moderate doses of ICS treatment.

The GINA guidelines recommended doses of ICS for asthmatic children treatment in figure 2 is variable and according with asthma symptoms.

*Figure 2. - Estimated Equipotent Daily Doses of Inhaled Corticosteroids for Children*

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* adapted from GINA Guidelines

The strategy to asthma symptoms control symptoms is quite similar, as we have used on adults, however LABA associated with medium dose of ICS on moderate and severe asthma is only recommend proceeding on children older than 5 years.

From 2 most used LABA, salmeterol and formoterol, only salmeterol has approval to be used in children under 12 years old.

Combination products containing an ICS and a LABA on association are preferred to those administered by separate devices.
During an acute asthma crises an MDI should be always used with a spacer due to some difficult to coordinate inhalation with actuation of the MDI.

We need to emphasise that the adherence to inhaled therapy on asthmatic children, mainly ICS, is very important.

Many factors could be responsible for this issue, such as ignorance on device use and management, socio-economic factors, educational level, stress and nowadays single parent situation.

Poor adherence and under-treatment can turn uncontrolled asthma.

**IMMUNOTHERAPY - ALLERGIC VACCINES**

Specific immunotherapy with allergens on presence of allergic asthma is indicated either adults or children, mainly when asthma is associated with allergic rhinitis.

Appropriate immunotherapy requires de identification and use of a single well defined and clinically relevant allergen.

Preferentially parenteral route is more used on adults and oral immunotherapy in children; however, parenteral route, by subcutaneous via, is more effective than oral and can be performed from childhood to adulthood.

The administration of specific immunotherapy should be monitored and performed, under control of a medical doctor specialist in allergology, because local and systemic adverse effects are not negligible.

**NEW TREATMENT**

The use of a novel asthma treatment as anti-IgE antibodies (Omalizumab), is a treatment option limited to patients with elevated serum IgE, but less 1000 U/l, and for patients with severe persistent asthma who are uncontrolled by ICS and LABA inhaled medication.
Further investigations are necessary regarding this alternative treatment, which is made by parenteral route and is very expensive.

Finally, we should always think that patients with mild asthma rarely see their doctor with symptoms of the disease.

Partly because of this situation, mild asthma is under-treated, which can “upgrade” to a real and more frequent symptomatic situation and progress to a moderate or severe asthma. A higher controller medication is associated with better asthma outcomes - symptoms, improvement of lung function, reduced exacerbations, reduced emergency hospital utilisation and better quality of life.

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