Universitat de Girona

IMPACT OF AN INTERVENTION ON PROINFLAMMATORY AGENTS IN ASTHMATIC PATIENTS

FINAL DEGREE PROJECT

Author: Natalia Kolakowska

Clinical tutors: Dr. Ramon Orriols and Dra. Gladis Sabater

Methodological tutor: Dr. Rafael Marcos Gragera

Faculty of medicine, University of Girona (UdG)

Girona, January 2019

I would like to express my most sincere gratitude to Dr. Ramon Orriols, Gladis Sabater and Rafael Marcos Gragera for helping me at developing this research project.

I would also like to thank the whole Respiratory Service of Hospital Universitari Josep Trueta of Girona for teaching me and receiving me so well.

Finally, I would like to thank my family and colleagues for all their help. None of this would be possible if it wasn't for them.

1 INDEX

2 Abstract 5
3 Abbreviations 6
4 Introduction 7
4.1 Prevalence 7
4.2 Pathophysiology 7
4.3 Risk factors 9
4.4 Clinical Features 11
4.5 Diagnosis 11
4.6 Classification of Asthma Severity 13
4.7 Treatment 13
4.8 Another type of treatment 15
4.9 Asthma control 16
5 Justification 19
6 Hypothesis 20
6.1 Primary hypothesis 20
6.2 Secondary hypothesis 20
7 Objectives 21
7.1 Main objective 21
7.2 Secondary objectives 21
8 Matherial And Methods 22
8.1 Study design 22
8.2 Population 22
8.3 Inclusion Criteria 22
8.4 Exclusion Criteria 22
8.5 Sample 23
8.5.1 Sample size 23
8.5.2 Sample selection 23
8.6 Variables 24
8.6.1 Independent variable 24
8.6.2 Dependent variable 24
8.6.3 Covariables 25
8.7 Measure instruments 28
8.8 Intervention 30
8.9 Data collection & study circuit 31

9 Statistical analysis 33
10 Ethical considerations 35
11 Strengths and limitations 36
12 Work plan 37
13 Study chronogram 38
14 Budget 39
15 Clinical and health care impact 40
16 Bibliography 41
17 Annexes 45
17.1 Annex 1: ACQ :Asthma Control Questionnaire 45
17.2 Annex 2: ACT: Asthma Control Test 47
17.3 Annex 3: AQLQ: Asthma Quality-Of-Life Questionnaire 49
17.4 Annex 4: TAI: Test of Adherence to Inhalers 51
17.5 Annex 5: Preliminary Questionnaire 52
17.6 Annex 6: Intervention 53
17.7 Annex 7: Informed Sheet for Participants 56
17.8 Annex 8: Informed Consent 58
17.9 Annex 9: Data Collection Sheet 59

2 ABSTRACT

Blackground: Asthma is one of the most common chronic diseases among the chronic respiratory disorders, affecting around 334 million people worldwide.

Exposure to different allergens and irritants has been shown to be a major source of asthma exacerbations and worsening of asthma symptoms.

Therefore, apart from the basal treatment, asthmatics can benefit from other non-pharmacological measures in order to avoid these proinflammatory agents.

Objective: The main purpose of this project is to evaluate the effectiveness of an intervention on proinflammatory agents for asthma exacerbations and asthma control.

Design: It will be a prospective, multicentre, pragmatical, controlled, randomized, open-label clinical trial.

Methods: Patients enrolled in this study will be randomized in two groups. The intervention group (n=124) will have an intervention in order to avoid proinflammatory agents and another intervention to improve treatment adherence, whereas the control group (n=124) will only have an intervention to improve treatment adherence.

We defined the primary outcome as the time to the first severe asthma exacerbation. Secondary outcomes will be number of exacerbations, time to the moderate exacerbation, changes in asthma quality-of-life and asthma control questionnaires, forced expiratory volume in 1 second (FEV_1), Oxid Nitric Exhalated (eNO), use of relief medication and treatment adherence.

Participants: Adults with a previous diagnostic of asthma, who had suffered ≥1 asthma exacerbation in the last year.

Key words: Asthma, asthma exacerbation, environmental measures, allergens, irritants.

3 ABBREVIATIONS

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AQLQ	Asthma Quality of Life Questionnaire
ENO	Oxid Nitric Exhalated
FEV_1	Forced expiratory volume in 1 second
GEMA	Guía Española sobre el Manejo del Asma
HEPA	High Efficiency Particulate Air
ICS	Inhaled corticosteroid(s)
IGE	Immunoglobulin E
LABA	Long-acting beta2 agonist(s)
NSAID	Nonsteroidal anti-inflammatory drug
SABA	Short-acting beta2 agonist (inhaled)
TAI	Test of Adherence to Inhalers
TH2	T cell helper 2

4 INTRODUCTION

Asthma is a common chronic inflammatory disease of the airway that is characterized with bronchial **hyperreactivity** to endogenous or exogenous stimuli, a variable **obstruction**, which can be totally or partially reversible, and an underlying **inflammation**.(1)

4.1 PREVALENCE

Asthma is an illness that has a universal geographical distribution and affects all the ages of life. Worldwide, the number of people suffering from asthma is estimated to be 334 million people.(2) In Spain, the European Community Respiratory Health Survey showed that the prevalence is heterogeneous among the autonomous communities, with more cases seen in coastal zones. For instance, in Barcelona it is 3% and in Huelva, it is 1%. It also concludes that the number of asthma patients is increasing overtime.(3)

4.2 PATHOPHYSIOLOGY

The principal pathophysiological events that exist in asthma are inflammation, airway hyperresponsiveness and bronchoconstriction.(4)

Asthma begins when a person, who is usually susceptible, has his first contact with an allergen or an irritant.(5)

- Allergen

The allergen liberates peptidases that damage the epithelium and allows them to enter and interact with the dendritic cells. Also, the epithelium releases different interleukins which facilitate the maturation of dendritic cells. After entering the lymphoid tissue, these cells activate and help to differentiate the lymphocytes T into T cell helper 2 (Th2) which liberates more interleukins.(5)

This ambient with cytokines promotes the production of immunoglobulin E (IgE) that interact with mast cells and immunize the person.(5)

The second time the person interacts with the allergen, the allergen directly contacts with the IgE-mast cell and activates different mediators that cause muscular constriction (bronchoconstriction), increased permeability, mucus secretion and recruitment of more inflammatory cells.(5)

Edema also plays a big part, especially in the pathogenesis of acute exacerbations and it is the result of inflammatory exudate. (1)

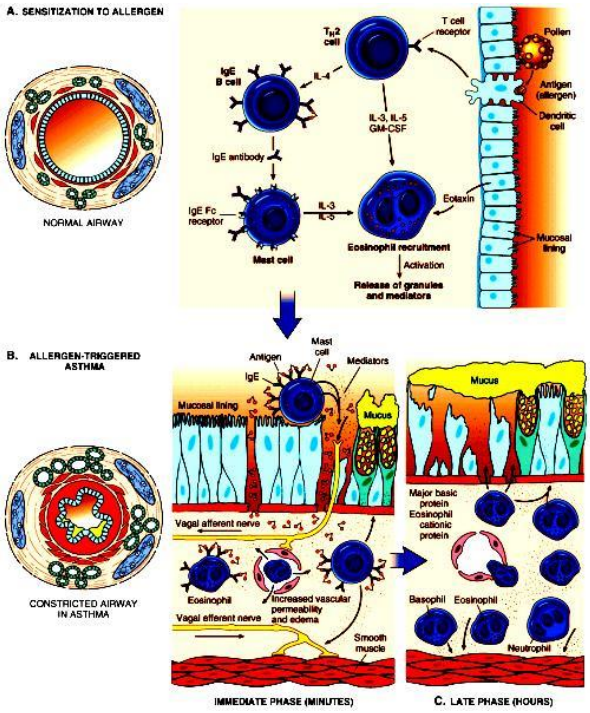


Figure 1. Pathophysiology (6)

Besides the acute inflammatory changes, there are also some structural changes as a result of chronic inflammation such as: hyperplasia and hypertrophy of the muscular layer, disruption of the bronchial epithelium which could explain why asthma patients are more sensitive to contamination as well as infections and allergens, and fibrosis of the basal membrane due to the accumulation of collagen III and V and eosinophils. (4,5)

Additionally, in the airway we can observe an increased number of goblet cells and a submucosal glands hyperplasia that provokes mucus hypersecretion, increasing bronchial obstruction. The blood vessels of the bronchi experience an increase in the blood circulation, also worsening the obstruction. Cholinergic nerves activation can be a consequence of the interaction with allergens, that causes stimulation of the secretion of mucus and bronchial constriction. (4,5)

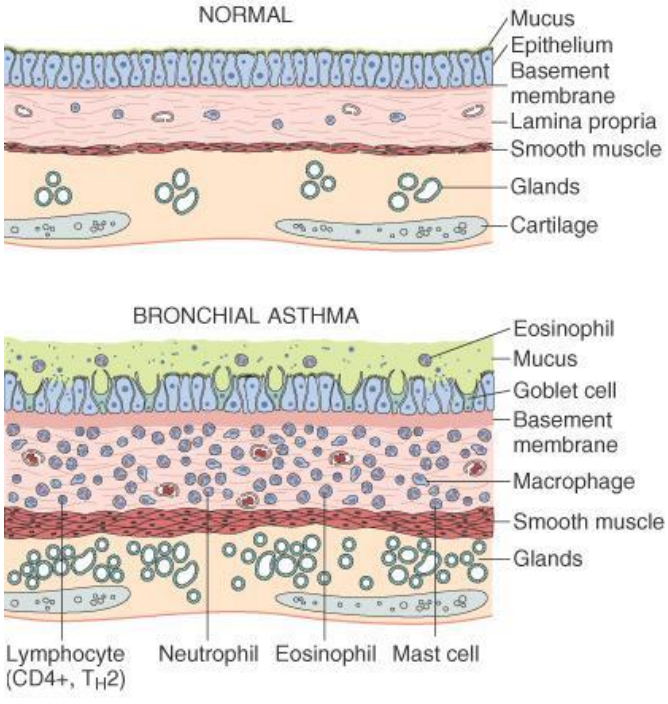


Figure 2. Histological changes in Asthma. (6)

- Irritant

When an irritant is inhaled, it causes an initial massive epithelial damage and a direct activation of sensitive nerves. Therefore, this combination results in inflammation of the airway with a concomitant increase in the vascular permeability and mucus secretion. (7)

As soon as we retire the harmful substance, the epithelium starts to recover. However, in some occasions, despite retiring the substance, the epithelium´s recovery is not always complete. (7)

4.3 Risk factors

There are different factors that can deteriorate or induce the symptoms of asthma:

- Allergens

Allergens are very common precipitants for asthma. Allergens can be found everywhere but dust mite allergen, mold and pet allergens are more frequently found in a house.

  - Mold: Exposure to mold can aggravate asthma and rhinitis.(8) There are around 60 species of mold but those with special concern are Penicillium, Aspergillus, Cladosporium and Alternaria. (9)
  - Dust mites: Some studies have shown that these could be a determinant for developing asthma (10), they multiply in warm weather with more than 50% humidity. (9)
  - Pets: The most frequent animals are cats and dogs but there are also others like hamsters and rabbits. It is well known that pets allergy is one of the most frequent asthma triggers. (11,12)
  - Pollen: According to *Sociedad Española de Alergología e Inmunología Clínica* (13) there are 8 million people allergic to pollen. The most frequent plants that cause pollen allergy are grass, olive trees and cypress trees.

- Virus, fungus, and bacteria

Viruses are the most common cause for asthma exacerbations, especially rhinovirus, the common cold virus. However, there are also other viruses like respiratory syncytial virus and parainfluenza that can trigger asthma exacerbations.(14)

- Tobacco

Daily tobacco exposure creates an increased airway inflammation, leading to hyperreactivity. Moreover, many studies have shown that environmental smoke is considered a risk factor for developing asthma. (15)

- Work

It is called occupational asthma, more than 300 substance are reported to act as an (7):

  - Allergen which requires a sensitization time. The most frequent occupational allergens are exposed in Table 1.

Animals	Laboratory workers, farmers, butchers, fishers
Latex, antibiotics	Health service
Mold and cereals	Bakers, farmers
Gums	Dental hygienist, printing
Metals (Nickel, Platinum, Zinc…)	Polishers
Isocyanates, Acid Anhydrides	Plastic, chemical industry

Table 1. Work allergens (7)

  - Irritant. Some of the principal agents are shown in Table 2.

Bleach, Ammonia, Sprays	Cleaning, treatment plant
Fire smoke	Fire brigade
Resins, acetic acid	Chemistry, cleaning

Table 2. Work irritants (7)

- Contamination, fumes from chimney and other fumes from the home
- Nonsteroidal anti-inflammatory drugs (NSAID)

The combination of nasal polyps, chronic sinusitis, and aspirin or other NSAID hypersensitivity is quite common and should be suspected when a patient suffers it. (1)

- Exercise

The diagnosis of asthma induced with exercise should be made with an exercise challenge test or an accurate clinical history.(1)

- Gastroesophageal reflux

Microaspirations and, consequently, a bronchospasm reflex is considered to be the mechanism. Even if the patient is asymptomatic, it can aggravate asthma, so monitorization of the intraoesophageal pH can sometimes be required.(16)

- Psychosocial factors

Stress is considered a risk factor for having asthma and a determinant for having a more severe asthma. (16)

4.4 Clinical Features

In general, this pathology has nonspecific symptoms, as a result, frequently it is underdiagnosed and, in consequence, it is unexpectedly undertreated. (17)

Symptoms are wheezing, cough, dyspnea or chest tightness. (18) It is also well known that personal history of atopy and family history of an atopic disorder such as parental eczema and asthma, are considered risk factor to develop future active asthma. (19)

4.5 Diagnosis

In adults, asthma diagnosis begins with the clinical history. The symptoms and risk factors like an atopic history or gastroesophageal reflux are likely to be asthma. In primary care, asthma is very often diagnosed with the clinical features. (20)

Confirmation is usually made with a pulmonary function test, most likely to be spirometry. (21)

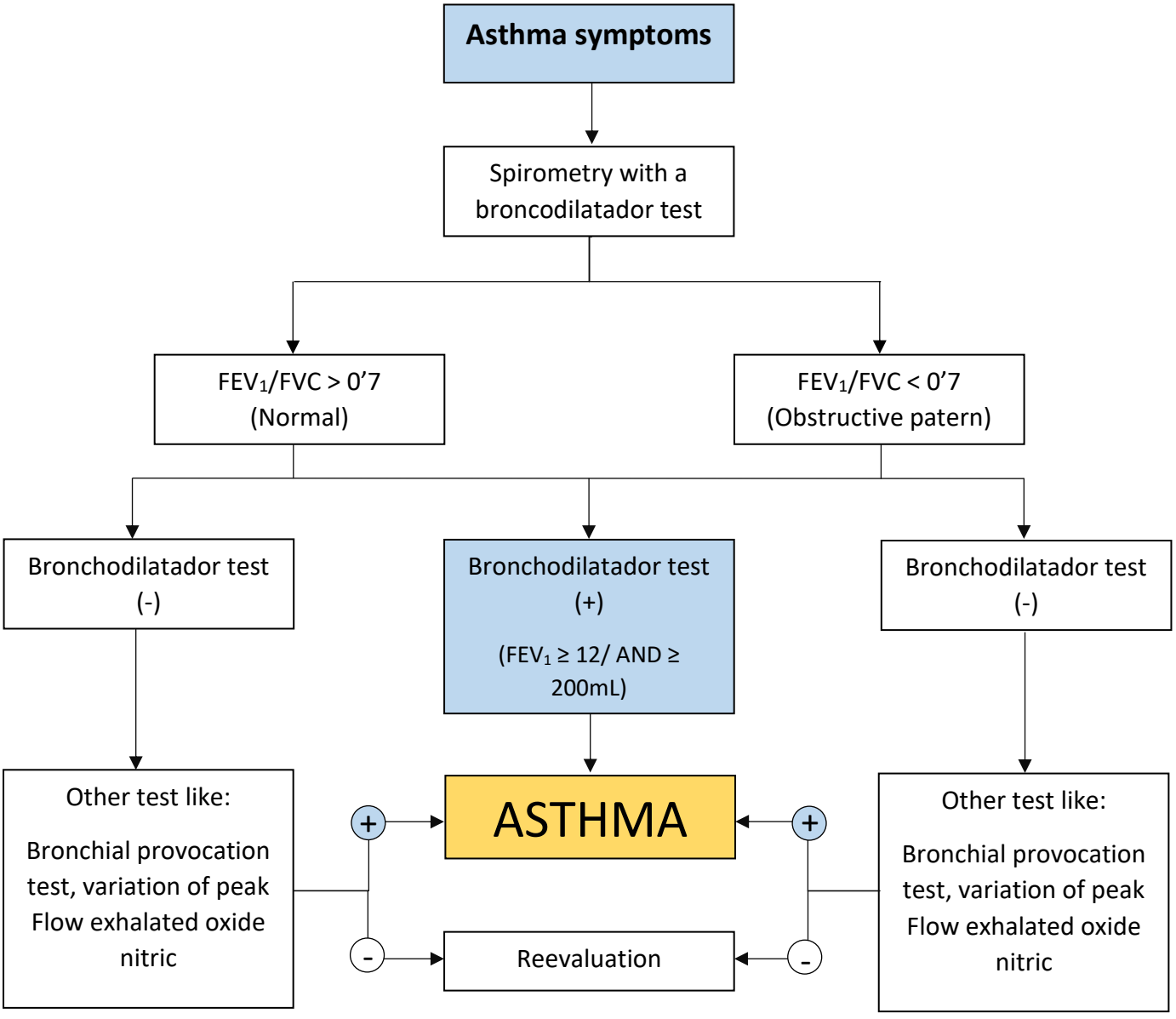
Spirometry is considered the best method in which we can identify airflow obstruction. Spirometry defines obstruction when forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio is less than 70%. (21)

Also, a bronchodilator, like salbutamol or terbutaline, can be used to see reversibility of the obstruction. Spirometry is repeated 10 minutes after giving the bronchodilator; when there

is a variation of FEV1 of 12% or more, together with an increase of the volume of 200 ml or more is considered positive for reversibility.

Asthma diagnosis is made with this positive result from the bronchodilator test. (21)

Whenever this test result is negative and there is firm suspicion of asthma, other tests can be made in order to find the diagnosis, for instance, bronchial provocation test, exhalated nitric oxide and variation of peak flow (1,21)



4.6 Classification of Asthma Severity

According to *La Guía Española del Manejo del Asma (GEMA)* (1), the asthma patient can be classified depending on their severity. This classification takes into account symptoms, exacerbations, the amount of medication used and pulmonary function tests. Therefore, patients are divided into 4 categories: intermittent, low persistent, moderate persistent and severe persistent (Table 3).

	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Daytime symptoms	No (≤2 times per week)	> 2 times per week	Every day	Constantly
*Relief medication (*short-acting beta 2 agonists**)**	No (≤ 2 times per week)	> 2 times per week but not daily	Every day	Several times in the day
Night symptoms	< 2 times per month	>2 times per month	>1 per week	Frequent
Activity limitation	No	Some	Quite	Many
Lung function **(FEV1 o PEF)** *% theoretical*	>80%	>80 %	> 60 % - < 80 %	≤ 60 %
Exacerbation	No	0 or 1 per year	≥ 2 per year	≥ 2 per year

Table 3. Asthma severity grade. Adapted from (1)

4.7 Treatment

There is no curative treatment for asthma, but symptoms can be controlled. This illness has two different kinds of medication (22):

- *Relievers* are used when the patient needs them. In general, short-acting β2 agonist (SABA) is the main drug inhaled. When the patient has an intolerance to SABA, inhaled ipratropium bromide can be used, but it is less effective.

- *Controllers* try to achieve an anti-inflammatory effect. They include inhaled glucocorticosteroids (ICS) or oral, leukotriene-receptor antagonist and anti-allergic or inhaled nonsteroidal agents, for instance, cromoglycate and nedocromil. These drugs are usually taken regularly and try to reduce exacerbations. The most common treatment in this category is ICS.

  Occasionally, ICS are used in combination with long-acting inhaled β2- agonists (LABA) in order to achieve asthma control.

Inhaled drugs are preferred for asthma treatment, in this way, patients suffer fewer systemic symptoms.

Asthma is treated depending on the severity of the disease (1):

- *Step 1: Reliever as-needed*.

  Usually, it is SABA.

- *Step 2: Low dose of daily ICS.*

  It is often used in persistent patients who have not received any medication. Another option can be a leukotriene-receptor antagonist.

- *Step 3: Low dose of daily ICS + inhaled LABA*

  In this step, a quick acting LABA like formoterol and low dose of ICS have been shown to be effective as a reliever and also as a controller.

- *Step 4: A medium dose of daily ICS + inhaled LABA*

  Another option is a medium dose of ICS+ leukotriene-receptor antagonist.

- *Step 5: High dose of daily ICS + inhaled LABA*

  Sometimes, a theophylline or leukotriene-receptor antagonist can be added to this treatment.

  When the patient does not respond to this treatment, he/ she can beneficiate from monoclonal therapy as an anti-immunoglobulin E (anti-IgE) (omalizumab).

- *Step 6: High dose ICS+theophylline/leukotriene-receptor antagonist+LABA*

Despite trying all the exposed treatment, badly controlled asthma can benefit from oral glucocorticosteroids.

	STEP1	STEP2	STEP3	STEP4	STEP5	STEP6
Controller	-	Low dose ICS	Low dose ICS+ LABA	Middle dose ICS+ LABA	High dose ICS+ LABA	High dose ICS+ theophylline/leukotriene antagonist receptor+ LABA
Reliever	SABA					

Table 4. Treatment of asthma. Adapted from (1)

4.8 ANOTHER TYPE OF TREATMENT

In addition to pharmaceutic treatment, physicians can recommend environmental measures that the patient can benefit from. The most common are:

- Smoking cessation

Smoking cessation has shown an improvement in the asthma-related quality of life, a reduction of usage of SABA, ICS, daytime symptoms and in bronchial hyperreactivity.(23) Environmental smoke also has its effects on asthma, this has been shown with a reduction in hospital admissions for asthma since the implementation of smoking-free legislations.(24)

- House dust mite allergen avoidance

Decreasing the humidity and other measures reduce the amount of allergens. There is conflict whether reducing house mite dust allergen alone (without any other environmental measure like pet removal or mold removal) has an effect on asthma. (25)

- Pet removal

Pet removal or domestic measures, when pet removal is not possible, reduce the amount of allergen. A prospective study showed that pets were one of the most potential modifiable risk factors for asthma exacerbation.(26)

- Mold removal

As we exposed before, mold spores can aggravate asthma, so different recommendations can be done to reduce them, for instance, repairing leaks and aggressive cleaning of moist areas.

- Pollen avoidance

Pollen allergen sensitization is very common. Although it is very difficult to control these allergens in high season, some measures can be implemented to reduce them, for instance, keeping the windows closed or staying indoors. (27)

- Occupational allergens/irritants avoidance

The best measure is to remove harmful substance or to change jobs. Nevertheless, many patients cannot, so masks or improved ventilation can be used. Reduction of symptoms and exacerbations is found, however, some patients do not improve despite these changes.(28)

- NSAID avoidance

NSAID can trigger fatal or near fatal asthma (29,30) Therefore, avoidance of these drugs, when there is an obvious clinical history or a positive provocation test, can have beneficial results.

4.9 ASTHMA CONTROL

To see if people suffering from asthma is well controlled, there are different aspects which can be explored in the medical consultation. For instance:

- The symptoms and their limitations to daily life and activity can be studied with a different test like Asthma Control Questionnaire (ACQ)(31) (see ANNEX 1) and Asthma Control Test (ACT) (see ANNEX 2) (32).
  The ACT is more preferable in daily clinical practice than ACQ, but neither of them is useful for uncontrolled asthma (33), so it is recommended not to use only these tests alone, but with other parameters to measure the control.
  To examine how the patient perceives his illness Asthma-related quality of life (AQLQ) (see ANNEX 3) can be used.
- Exacerbation or the use of the emergency department

- Lung function (the most used parameter is the decline of FEV1). FEV1 alone cannot predict if asthma is controlled or not, but the evolution of FEV1 can give valuable information.

  Pre-FEV1 is considered the parameter that is done without bronchodilator whereas Post-FEV1 is the parameter found 15 minutes after a bronchodilator. Both of them can change with treatment and can predict the illness activity.(20)
- Treatment adherence. This can be measured seeing with an accurate anamnesis, the last prescription in the pharmacy and Test of the Adherence to Inhalers (TAI) (see ANNEX 4) (1)
- Oxid Nitric exhaled (eNO). This non-invasive test measures the inflammation of the airway. Recently, the reunion of Asthma Meeting Point considered eNO a valid parameter that could contribute to assess asthma control.(34)

The guidelines *of Global Initiative for Asthma* (21) *and GEMA*(1) offers a classification depending on the response of the medical treatment. Patients can be classified in: well controlled, partly controlled and uncontrolled (Table 5).

	Controlled *(all of the following)*	**Partially controlled** *(Any of these categories in any week)*	**Badly controlled**
Daytime symptoms	0-2 times per week	> 2 times per week	Yes if three or more characteristics of asthma partly controlled
*Relief medication (*short-acting beta 2 agonists)	No	> 2 times per week	
Evening symptoms	No	Yes	
Activity limitation	No	Yes	
Lung function **- FEV1** **- PEF**	> 80 % of the theoretical value > 80% of the best personal value	< 80% of the theoretical value < 80% of the best personal value	
Exacerbation	Not one	> 1 per year	≥ one any week

Table 5. Classification of the control of asthma. Adapted from (1)

3.10 Exacerbations

Exacerbation is an acute or subacute episode of asthma in which there is a worsening of asthma symptoms, for example, chest pain or dyspnea. Another aspect that happens is the decrease of the expiratory flow (FEV1 or PEF). (35)

Depending on the speed, exacerbations can be divided into two: those with a rapid onset (less than 3 hours) and those with a slow onset. Slow onset exacerbations suggest to be caused by an upper respiratory tract infection, meanwhile, rapid onset exacerbations are produced by allergens or stress.(29)

According to *the American Thoracic Society,* exacerbations can be differentiated in(20):

- **Severe exacerbations**: It is defined as the one that needs administration of systemic corticosteroids or an increase from a stable maintenance dose, for at least 3 days or the one that requires emergency room visits and/or hospitalizations or unscheduled doctor visits.
- **Moderate exacerbations**: It is considered as the one in which the patient has deterioration in symptoms, lung function and requires an increased rescue bronchodilator use. These features should last at least 2 days.

5 JUSTIFICATION

Asthma is one of the most common chronic diseases and its prevalence is increasing. (3) The disability-adjusted life years, a parameter which combines morbidity and mortality, is considered to be similar to that of schizophrenia, diabetes and cirrhosis.(36) Moreover, the cost of asthma is estimated to exceed that of tuberculosis and HIV combined. (37)

Some asthma exacerbations risk factors are mold, house dust mites, animal dander and irritants. Although a better understanding of the causes of asthma and asthma exacerbation is needed, environmental interventions like mold removal, pet removal and vacuuming seem to have an effect on the burden of the disease and the number of exacerbations. (1,21,22)

While many studies have assessed these procedures for one risk factor and did not show an improvement in the clinical features of asthma, results from multicomponent interventions that combine avoidance of more than one risk factor have shown a beneficial effect on asthma. (38,39) However, these studies are lacking and are only done inside the houses. Studies which implement avoidance measures in other settings where the patient is also routinely exposed to allergens and irritants, such as the workplace, are not reported.(39)

Many of these studies have focused on paediatric population (40), but the number of studies done in adults is extremely small and inconclusive. Furthermore, the vast majority of the studies done do not report the results with standardised questionnaires for asthma control, asthma quality of life and exacerbations, so a more precise understanding of the impact these interventions have is needed. (39,41)

Additionally, the health and economic consequences can be beneficial for asthmatic patients; for instance, they could have fewer hospitalizations, fewer medication, fewer health visits and less absenteeism from workplace. Moreover, an estimation of the economic benefits from these multicomponent interventions have shown to exceed the program costs. (42)

This situation emphasizes the need for more studies looking for effectiveness of multicomponent interventions focusing on education and avoidance of asthma proinflammatory agents.

6 HYPOTHESIS

6.1 PRIMARY HYPOTHESIS

An intervention on proinflammatory agents in asthmatic patients **increase the time to the first severe asthma exacerbation** compared to the control group.

6.2 SECONDARY HYPOTHESIS

Proinflammatory agents avoidance intervention:

- Reduce the number of patients' exacerbations.
- Increase the time to the first moderate exacerbation.
- Improve their asthma quality-of-life.
- Improve asthma control.
- Reduce the utilization of relief medication.

All compared with a control group.

7 OBJECTIVES

7.1 MAIN OBJECTIVE

This study aims to quantify and compare **the time to the first severe asthma exacerbation** in an intervention group in which proinflammatory agents are avoided and in a control group.

7.2 SECONDARY OBJECTIVES

To evaluate and compare between the intervention group and the control group:

- The number of patients who suffer a severe exacerbation, which is defined as a patient who needs hospitalization or emergency department attendance, use of systemic corticosteroids or an increase dose from a stable maintenance dose for at least 3 days. It is a discrete quantitative variable.
- Time until the first moderate exacerbation which is defined as the one with deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use. These features should last >2 days and do not need more doses of corticosteroids.
- Number of patients who present a moderate exacerbation
- Number of total exacerbations, severe and moderate
- The quality of life.
- Control of asthma.
- Pre and post-FEV1 (spirometry)
- Exhaled nitric oxide (eNO)
- Treatment adherence
- Utilization of relief medication.

8 MATHERIAL AND METHODS

8.1 STUDY DESIGN

This study is designed as a prospective, multicentrer, pragmatical, randomized controlled clinical trial that takes part in primary care centers and hospital attention.

8.2 POPULATION

The target population of this study are adult patients with a previous asthma diagnosis who attend primary care centers or Pneumology Department of Hospital Santa Caterina or Hospital Universitari Josep Trueta.

8.3 INCLUSION CRITERIA

- Adults patient (>16 years).
- Patients with a previous diagnosis of asthma.
- Patients with an ICS treatment with or without an additional treatment.
- Patients who have had ≥ 1 severe or moderate exacerbation in the last 12 months.

8.4 EXCLUSION CRITERIA

- Smokers or previous smokers of >10 cigarette packs.
- Patients who are in a pharmaceutic study.
- Patients with another pulmonary problem like sleep apnea or bronchiectasis.
- Patients with a history of a severe chronic illness.
- Patients with an exacerbation in the last 4 weeks before the inclusion in the study.

8.5 SAMPLE

8.5.1 Sample size

Based on a previous study, we estimated that 65% of the participants in the placebo group would experience an asthma exacerbation (hazard ratio of 0.65) (43) In the intervention group, we considered the rate of first exacerbation of 30% to be clinically relevant (hazard ratio of 0.7). We also consider the expected drop-out to be 10%.

Therefore, assuming an alpha risk (α) of 0.05 and a beta risk (β) of 0.2 in a bilateral contrast, we will need 124 patients in each group (a total of 248 participants) in order to detect these differences.

The free online application GRANMO has been used to calculate the sample size. (44)

8.5.2 Sample selection

Sample selection will consist in a non-probabilistic consecutive sampling in order to choose our patients. This method consists on inviting all available patients that are being visited in one of the centers and accomplish all the inclusion and exclusion criteria.

We estimated a recruitment time of 4 months in which 3 participants per day will be recruited.

The sample will be composed of 2 groups:

- The first group *(Protocol group)*: Composed of patients meeting all inclusion criteria and none of the exclusion criteria. This group will have a specific intervention to avoid different allergens and irritants according to a questionnaire (see ANNEX 5) and IgE-profile. Moreover, improvement of treatment adherence will also be carried out.
- The second group (*Control group*): Composed of patients meeting all inclusion criteria and none of the exclusion criteria before the implementation of the protocol. In this group, adherence to asthma treatment will be assessed, alongside with an improvement of it.

Patients will be randomly assigned to either the control group or the intervention group using a blocked randomization within a site.

8.6 VARIABLES

8.6.1 Independent variable

The independent variable of this study will be the intervention to avoid some of the most important allergens and irritants. The intervention will be focused on avoidance of dust mite, passive smoking, pets, mold, NSAID and occupational exposure. The intervention will be tailored to each patient IgE-sensitization profile and a questionnaire of environmental exposures.

It is a nominal qualitative dichotomous variable (Intervention/No intervention).

8.6.2 Dependent variable

As the main dependent variable, we will use the effectiveness of the intervention. We will consider our intervention effective when the time to the first severe exacerbation is more prolonged than in the control group. It is a continuous quantitative variable.

The secondary dependent variables of this study are:

A. The number of patients with a severe exacerbation, which is defined as a patient who needs hospitalization or emergency department attendance, use of systemic corticosteroids or an increase dose from a stable maintenance dose for at least 3 days. It is a discrete quantitative variable.
B. Time until the first moderate exacerbation, which is defined as the one with deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use. These features should last >2 days and do not need more doses of corticosteroids.
   It is a continuous quantitative variable.
C. Number of patients who present a moderate exacerbation. It is a discrete quantitative variable.
D. Number of total exacerbations (severe and moderate). It is a discrete quantitative variable.
E. Measurement of the quality of life. It will be assessed with the short Spanish version test of Asthma Quality of Life Questionnaire (AQLQ) (see ANNEX 3). (45). The overall score is the mean of the 15 questions. It is a continuous quantitative variable.

F. Measurement of the control of asthma. It will be assessed with the test Asthma Control Test (ACT) (see ANNEX 2) (32). It is a quantitative discrete variable.
G. Spirometry. Pre and postFEV1: It is measured in percentage. It is a continuous quantitative variable.
H. Exhaled nitric oxide (eNO) It is measured in percentage. It is a continuous quantitative variable.
I. Measurement of treatment adherence. The test used will be Test of Adherence to Inhalers (TAI) (ANNEX). It is a quantitative discrete variable.
J. Utilization of relief medication. It will be expressed in times of relief medication utilization. It is a discrete quantitative variable.

8.6.3 Covariables

As our study will be randomized, we do not expect confounding variables. However, whenever there is a residual confounding, for instance, when there is aggrupation of participants with certain characteristics, we will control it with the following covariables:

- Age: It will be measured in years. It is a continuous quantitative variable.
- Gender: It is a nominal qualitative variable (Male / Female / Unknown).
- Smoking: Smokers are not included in this study. It is also nominal qualitative variable (Non-smoking/ Ex-smoker/ Passive smoker).
- Basal glucocorticoid treatment: It is a polytomous ordinal qualitative variable (Low dose < 400 mcg/ Middle dose 400-800 mcg/ High dose >800mcg).
- Environmental exposures. It will be divided in each environmental exposure: air pollution, mold, NSAID, pet, passive tobacco, house dust mite, pollen and work allergens-irritants. It is a nominal qualitative variable (Yes exposed/ No exposed).
  Air pollution will be measured with daily mean levels of different particles like nitrogen oxides, carbon monoxide and sulfur dioxide. It is a continuous quantitative variable.
- IgE-sensibilization. It will be divided in: dog allergen, cat allergen, dust mite allergen and mold. It is a nominal qualitative variable (Yes sensitive/ No sensitive).
- Socio-economic variables proxied by education and occupation. It is a polytomous qualitative variable.

Variables	Type of data	Measure instrument	Categories or values
Intervention	Categorical dichotomous	No measuring method needed	Intervention No intervention
Time to first severe exacerbation	Continuous quantitative	Anamnesis	Number of days
Number of patients with a severe exacerbation	Discrete quantitative	Anamnesis	Number of patients
Time to first moderate exacerbation	Continuous quantitative	Anamnesis	Number of days
Number of patients with a moderate exacerbation	Discrete quantitative	Anamnesis	Number of patients
Number of total exacerbations	Discrete quantitative	Anamnesis	Number of patients
Asthma quality of life	Continuous quantitative	AQLQ	Mean of the 15 questions
Asthma control	Discrete quantitative	ACT	<23→Asthma not controlled 20-24→Good asthma control >26→Total asthma control
Pre-$FEV_1$and post-FEV_1	Continuous quantitative	Spirometry	Percentage
Exhaled nitric oxide	Continuous quantitative	Exhaled nitric oxide	Percentage

Treatment adherence	Discrete quantitative	TAI	=50 points→Good adherence 46-49→Intermediate adherence ≤45→Poor adherence
Relief medication	Discrete quantitative	Anamnesis	Number of times of relief medication utilization
Age	Continuous quantitative	Anamnesis	Number of years
Gender	Nominal qualitative	Anamnesis	Male Female
Smoking	Nominal qualitative	Anamnesis	Non-smoking Ex-smoker Passive smoker
Basal glucocorticoid treatment	Polytomous ordinal qualitative	Anamnesis	Low dose (<400mcg) Middle dose (400-800mcg) High dose (>800mcg)
Enviromental exposure (divided in: NSAID, passive smoking house dust mite, pollen, occupational, air pollution and pet)	Nominal qualitative *Air pollution is continuous quantitative	Questionnaire	Yes exposed No exposed *Daily mean levels of air pollution
IgE sensibilization	Nominal qualitative	Blood test	Yes sensitive No sensitive
Socio economic variables	Polytomous qualitative	Anamnesis	Low Middle High

Table 6. Variables of the study

8.7 MEASURE INSTRUMENTS

- *Questionnaire*. A self-created questionnaire has been specially designed for this study (see ANNEX 5) to detect allergens and irritants. The survey proposed is a simple, brief and easily understood instrument. It consists of 13 questions asking for different exposures. The questionnaire design will be developed in 3 phases:
    - *1st Phase:* A review of literature and the clinical experience of researchers will be used to perform the questionnaire. Based on this, a self-administered and structured questionnaire is designed for the participants of the study.
    - *2nd Phase.* The questionnaire will need internal consistency, test-re-test and validity.
        - Internal consistency means that the different items have a correlation and can be grouped. The internal consistency will be evaluated with the Cronbach α value and all the items will have an α>0.7
        - Test -retest reliability measures stability of an instrument over time with repeated testing. It is done in two different occasions and the results should be the same.
        - Validity indicates if the instrument appears to be assessing the desired qualities. Delphi technique will be used, it consists of submitting the questionnaire to the assessment of the experts who need to evaluate the ability of all the dimensions that we want to measure. The recommended number of experts is 6, but there is no consensus. (46)
    - *3rd Phase:* The questionnaire will be distributed to the participants of the project.

- *Blood test: Immunoglobulin E* An hemogram, total IgE and specific IgE will be done. The specific IgE measured will be:
    - Cat dander
    - Dog dander

- *Dermatophagoides farine*
- *Dermatophagoides pteronyssinus*
- *Alternaria alternata*
- *Aspergillus niger*
- *Aspergillus fumigatus*
- *Cupressus arizonica*
- *Cupressus sempervivens*
- *Platanus acerifolia*
- *Olea europea*
- *Parietaria judaica*
- *Parietaria officinalis*
- *Plantago laceolata*
- *Artemisa vulgaris*
- *Secale cereal*

- *Spirometry* is one of the most common pulmonary tests, it is used to evaluate and monitor pulmonary function. Spirometry will be done according to the guidelines of the American Thoracic Society (47) within a Silbemed® model.

  Before starting, the test should be explained to the patient and collaboration should be stressed. The patient will be sitting, without crossing his/her legs and the back must be constantly supported in the backrest.

Figure 3. Spirometry

After placing the mouth in the mouthpiece, the patient will breath calmly for at least 3 breaths. Then, he/she will be asked to:

- Breath in as much air as possible for 1s (pre-FEV1 will be obtained with this manoeuvre).
- Blow fast.
- Prolong the expiration without pause for 6s.

To perform a postbronchodilator test, a bronchodilator should be given, for instance, salbutamol (4 inhalations of 10 mcg) or ipratropium bromide (if salbutamol is

contraindicated, 4 inhalations of 22mcg). Then, after 10 minutes, the same manoeuvres should be done again (pos-FEV1 will be obtained).

- *Exhaled nitric oxide* (eNO) It is a test used to measure inflammation in the lungs. To do this test the patient should have not eaten or drunk for at least one hour before, and alcohol, caffeine and tobacco should have been avoided for at least 24 hours before. The patient will be sitting, and he/she will be asked to breathe in for 5 seconds and then exhale steadily. A Niox vero® model will be used.

- *AQLQ* (see ANNEX 3) (45) It is a test with 15 validated questions that goes from 1 to 7 (in which 1 is the highest degree of disability and 7 is the best level of autonomy). The questions can be classified in 4 areas: symptoms, environmental stimuli, emotional function and activity limitation.

- *TAI* (see ANNEX 4), which is used in asthma and Chronic Obstructive Pulmonary Disease, it identifies the degree of adherence and the type of non-compliance. It is a test with 12 questions in which the first 10 questions will be answered by the patient and the last 2 questions by the healthcare professional.

- *ACT* (see ANNEX 2) It measures the control of asthma. It consists of 5 questions with a 4 week recall on symptoms and daily functioning with a 5-point scale from 1=all day to 5=completely controlled. The total scale goes from 5 “poor controlled asthma” to 25 “completely controlled asthma”.

8.8 Intervention

Patients will be randomly assigned to either the control group or the intervention group by blocked randomization within a site.

- Protocol group: This group will have a specific intervention to avoid different allergens and irritants according to a questionnaire (see ANNEX 5) and IgE-profile. Moreover, improvement of treatment adherence will also be another aim.
- Control group: In this group, adherence to asthma treatment will be assessed, alongside with an improvement of it.

The goal of the intervention is to provide skills, knowledge and motivation in order to perform an intervention on proinflammatory agents. Our project is based on the social learning theory. (48) This theory emphasizes that behaviour can be changed with the persons´ attitude and expectations.

It is important to highlight that all the participants cannot change his/her basal treatment or start immunotherapy and that the use of reliever medication is always allowed.

The recommendations are exposed in the ANNEX 6 and are based on the *Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica.*(27)

8.9 DATA COLLECTION & STUDY CIRCUIT

For data collection we will contact the physicians working in the primary centers of Girona. We will inform them about our study, and we will ask for their collaboration in order to work together with the Respiratory Department in Hospital Doctor Josep Trueta and Hospital Santa Caterina for data collection.

The study circuit is described below:

- Patient recruitment: All the patients with a previous asthma diagnosis, that come to the Respiratory Department or to Primary Care Centers, will be evaluated to see if they meet all the inclusive and none of the exclusive criteria. Researchers will explain the study and an Information Sheet for Participants (see ANNEX 7) will be given.
- 1st Appointment: There will be a resolution of patients´ doubts and verification of the patients´ understanding of the project will be assessed. Then, if the patient agrees to participate in the project, Informed Consent Form (see ANNEX 8) will be signed and different tests will be done: mini AQLQ, ACT, TAI, spirometry, eNO, Blood test (Hemogram, total IgE and specific IgE).
- 2nd Appointment: Randomization will be done within a website and two groups will be formed: the intervention group and the control group. In both groups, a questionnaire about allergens and irritants (see ANNEX 5) will be answered.
    - In the intervention group, specific environmental measures will be recommended (see ANNEX 6) depending on what the participant is sensitive

to and their exposure. Moreover, treatment adherence education will be also carried out.

  - In the control group, only treatment adherence education will be carried out.

- 3º Appointment: *1 month.*
  - In the intervention group, the questionnaire, specific environmental measures and treatment adherence education will be given.
  - In the control group, treatment adherence education will be carried out.
- 4º Appointment: *3 months.*
  - In the intervention group, the questionnaire, specific environmental measures and treatment adherence education will be given.
  - In the control group, treatment adherence education will be carried out.
- 5º Appointment: *12 months.* In both groups, different tests will be assessed: the questionnaire, mini AQLQ, ACT, TAI, spirometry, eNO and a Blood Test (Hemogram, total IgE and specific IgE).

9 STATISTICAL ANALYSIS

The statistical analysis will be executed using Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, NY, US). An intention-to-treat analysis will be performed. For missing data results of the last visit will be used.

Descriptive analyses

The result of our qualitative variables will be expressed as proportions (percentage) stratifying by the intervention and control group.

For the quantitative variables, they will be expressed as a mean +/- standard deviation (SD) in case they have a symmetric distribution (i.e. normal variables). For variables with asymmetric distribution (discrete variables), median and interquartile range (IQR) will be used. Again, always stratifying by the intervention and control group.

For the dependent variables in which time intervenes, we will estimate and represent in survival curves (Kaplan-Meier estimator), stratifying in intervention and control group.

Bivariate inference

The comparison of proportions of quantitative variables between the intervention group and control group will be done with a Chi-square (x2) test or Fisher exact test when the expected frequency is less than 5.

The comparison of means and medians between the intervention and control group will be done with a t- Student test and Mann-Whitney U test respectively.

The comparison between survival curves will be done with a log-rank-test.

Multivariate analysis

The association between the intervention and dependent variables will be assessed with regressions, adjusting the covariables explained before.

When the dependent variable is continuous, we will use a linear regression.

When the dependent variable is discrete, we will use a Poisson regression, in which risk relative and their confidence intervals will be measured.

In dependent variables in which time intervenes, a Cox proportional Hazard regression analysis will be done. We will measure Hazard rations and their confidence intervals.

The results will be considered statistically significant at a value of $p<0.05$ with a confidence interval of 95%.

10 ETHICAL CONSIDERATIONS

All patients in this study will receive treatment and follow-up according to the most recent clinical guidelines of asthma. The extra measurements that the patients will receive are non-invasive and do not mean a risk or discomfort for the patient.

The present study will be conducted according to the requirements expressed in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects* signed by the World Medical Association in 1964 and last revised in October 2013.

A patient will not enter the study until he/she has been properly informed, has been given time to contemplate *participation* and has freely given his/her consent by reading and signing the informed consent (see ANNEX 8). This will be done prior to performing any study-related procedures. Patient autonomy will be respected, not only before entering the trial but always. Approval of the protocol before its implication will be done by the Committee for Ethics and Clinical Research at the Catalan Health Institute and will be based on the Organic Law 14/2007 of the 3th of July on Biomedicine Research.

Patient data anonymity will be guaranteed to preserve patient confidentiality. Patient anonymity and rights will be based on the Organic Law 03/2018 of the 5th of December on the Protection of Data, the Basic Law 41/2002 on the autonomy of the patient and rights and obligations regarding to clinical information and documentation and the Royale Decree 1090/2015, of the 24th of July, on Biomedical Research.

All investigators of this study will have to declare a conflict of interest if they exist.

11 STRENGTHS AND LIMITATIONS

There are some potential limitations that should be considered because they can interfere in our research:

- One of the main limitations of the study consists of being an open-label trial. Therefore, ascertainment or detection bias is present due to a lack of blindness. Double blind or single blind experimental design is certainly not possible because it is easy for the patient to perceive the intervention that he/she is part of, so differences between them are present and perceptible to both patients. To try to reduce it, our main dependent variable is as objective as possible (time till the first severe exacerbation) in order to increase internal validity.

- Another limitation is the lack of homogeneity in the intervention among the participants, in which patients will not perform the same recommendations. Moreover, we cannot evaluate which recommendation is the most helpful for a better asthma control.
  Also, although the severity of sensitization does not precisely identify with asthma outcomes, there will be variability in patient's response to the intervention.

- In order to avoid selection bias, we have decided to include all the primary care centers of Girona for the sample recruitment. This gives us another advantage because each health professional who will participate in our study will have to recruit fewer participants.

- Hawthorne effect could be present as the patients feel they are studied.

- There is no control to see whether the intervention decreases allergens and irritants levels.

- To design a prospective study has the risk that patients can leave it due to lack of compliance. However, this is not expected to create problems because it has been taken into account when the sample size was estimated.

12 WORK PLAN

Stage 0: Study design

- *November-January 2019*
- This stage is already done. We have done the bibliographic research and protocol design

Stage 1: Ethical evaluation and questionnaire validation

- *February 2019*
- The protocol will be processed in order to indentify possible stayistical errors, misspellings and other mistakes.
- The questionnaire will be validated.
- Presentation of the protocol to Clinical Research Erhics Commmitee at Hospital Universitari Doctor Josep Trueta for its approval.

Stage 2: Coordination

- *March 2019*
- We will do the first meeting of the research team to organize tasks, clarify different phases of the study with the chronogram and review the roles of each participant. The whole research team will keep in contact via e-mail and/or telephonic messages.

Stage 3: Patients´recruitment

- *April 2019- July 2019*
- Patients previously diagnosed with asthma will be investigated in order to see if they meet the inclusion criteria. In case the patient is apt to enter the study, the investigation will be explained and all the information necessary given.

Stage 4: Intervention and data collection

- *August 2019-July 2020*
- Intervenition will be carried out in this period. Data from each group will be compiled and refined in order to prepare it for statistical analysis

Stage 5: Statistical analysis

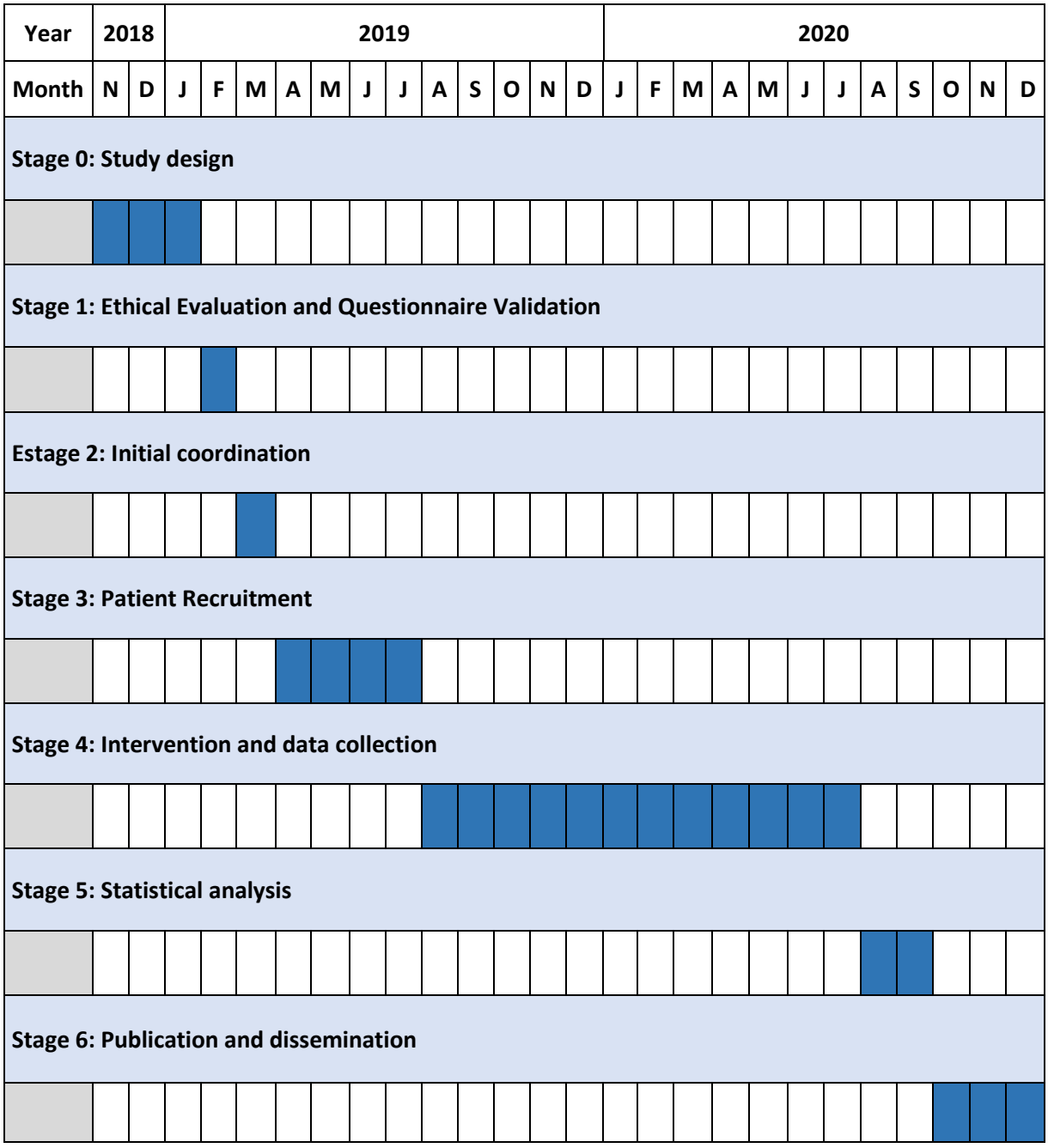
- *August 2020-September 2020*
- A qualified statician will analyse the data with a proper statistical test.
- The research team will keep in contact and meet in order to analyse, interpret and discuss the results.

Stage 6: Publication and dissemination

- *October 2020-December 2020*
- Articles will be send to different national and international journals for their publication.
- We will attempt to display our results in congresses and conferences.
- This will be carried out by the principal investigators.

.

13 STUDY CHRONOGRAM



14 BUDGET

Expenses			Cost
1. Personal expenses			**0 €**
2. Executive expenses			
	2x Spirometry (14€)	*2(14 x 248 patients)*	**6.944 €**
	2x FeNo (20€)	*2(20 x 248 patients)*	**9.920 €**
	2x Blood Test: Immunoglobulin E (120€)	*2(120 x248patients)*	**59.520 €**
	Printing and other materials	*X*	**200 €**
	Nursery	*20h/€ x 6h x 248 patients*	**29.760 €**
	Statistical Analysis	x25h	**875 €**
3. Publication and dissemination expenses			
	Scientific Publication		**1.000 €**
	Attendance to scientific meetings and congress		**1.000 €**
Total			**109.219 €**

15 CLINICAL AND HEALTH CARE IMPACT

This study can change the way we manage asthma. If our hypothesis is confirmed, the non-pharmacological asthma treatment could gain more importance. Therefore, patients could benefit from fewer medication intake, fewer exacerbations, better health conditions, and consequently, better asthma related quality of life.

Moreover, we will also have a better understanding of the impact these measures have on asthma related quality of life, asthma control and exacerbations.

Finally, this study can help with public health costs as patients will need less medication and health care utilization, and a reduction in mortality and workplace absenteeism could be found.

16 BIBLIOGRAPHY

1. GEMA 4.3. Guía española para el manejo del asma [Internet]. 2018 [cited 2018 Dec 14]. Available from: http://www.luzan5.es

2. Global Asthma Network The Global Asthma Report [Internet]. 2014 [cited 2018 Dec 14]. Available from: www.globalasthmanetwork.org

3. Urrutia I, Aguirre U, Sunyer J, Plana E, Muniozguren N, Martínez-Moratalla J, et al. Cambios en la prevalencia de asma en la población española del Estudio de Salud Respiratoria de la Comunidad Europea (ECRHS-II). Arch Bronconeumol [Internet]. 2007 Aug 1 [cited 2018 Dec 19];43(8):425–30. Available from: http://linkinghub.elsevier.com/retrieve/pii/S030028960771102X

4. Barnes J. Asma. In: Kasper, Dennis; Fauci, Anthony ; Hause, Stephen; Longo, Dan; Jameson, J. Larry; Loscalzo J, editor. Harrison Principios de Medicina Interna,. 19th ed. Madrid; 2015. p. 1–13.

5. Nuria Renata; Jiménez Vargas, Mariela; Salinas Miralles E. Investigación y ciencia. Investig Cienc [Internet]. 2015 [cited 2018 Dec 15];23(65). Available from: https://www.redalyc.org/html/674/67443217009/

6. What's More to Learn with Bronchial Asthma? /Little doctors [Internet]. 2011 [cited 2019 Jan 10]. Available from: https://littlemds.wordpress.com/2011/01/12/chronic-obstructive-pulmonary-disease-bronchial-asthma/

7. Orriols Martinez R, Abu Shams K, Alday Figueroa E, Galdiz Iturri JB, Isidro Montes I, Muñoz Gall X, et al. Normativa del asma ocupacional. Arch Bronconeumol [Internet]. 2006 [cited 2018 Dec 28];42(9):457–74. Available from: http://www.archbronconeumol.org/es-pdf-S0300289606706895

8. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an Aeroallergen as a Possible Precipitating Factor in Respiratory Arrest in Young Patients with Asthma. N Engl J Med [Internet]. 1991 Feb 7 [cited 2018 Dec 29];324(6):359–63. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199102073240602

9. Germania A. Pinheiro, MD, MSc P. Environmental Triggers of Asthma [Internet]. 1st ed. ATSDR; 2016 [cited 2018 Dec 25]. Available from: http://www.atsdr.cdc.gov/csem/conteduc.html

10. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to House-Dust Mite Allergen and the Development of Asthma in Childhood. N Engl J Med [Internet]. 1990 Aug 23 [cited 2018 Dec 26];323(8):502–7. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199008233230802

11. Almqvist C, Wickman M, Perfetti L, Berglind N, Renstron A, HEDRÉN M, et al. Worsening of Asthma in Children Allergic to Cats, after Indirect Exposure to Cat at School. Am J Respir Crit Care Med [Internet]. 2001 Mar 14 [cited 2018 Dec 27];163(3):694–8. Available from: http://www.atsjournals.org/doi/abs/10.1164/ajrccm.163.3.2006114

12. Takkouche B, González-Barcala F-J, Etminan M, FitzGerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. Allergy [Internet]. 2008 Jun 28 [cited 2019 Jan 15];63(7):857–64. Available from: http://doi.wiley.com/10.1111/j.1398-9995.2008.01732.x

13. Portal SEA: Infografía Alergia al Polen [Internet]. 2014 [cited 2019 Jan 15]. Available from: https://www.seaic.org/inicio/guia-farmacoterapeutica-de-inmunoterapia/infografia-alergia-al-polen

14. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: Origin, effect, and prevention. Am Acad Allergy [Internet]. 2011 [cited 2019 Jan 15];128(6). Available from: https://www.siaip.it/upload/Asthma exacerbations.PDF

15. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. Asthma and Wheezing in the First Six Years of Life. N Engl J Med [Internet]. 1995 Jan 19 [cited 2018 Dec 18];332(3):133–8. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199501193320301

16. Lemanske RF, Busse WW. Asthma. J Allergy Clin Immunol [Internet]. 2003 Feb 1 [cited 2018 Dec 22];111(2 Suppl):S502-19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12592297

17. van Schayck CP, van Der Heijden FM, van Den Boom G, Tirimanna PR, van Herwaarden CL. Underdiagnosis of asthma: is the doctor or the patient to blame? The DIMCA project. Thorax [Internet]. 2000 Jul 1 [cited 2019 Jan 8];55(7):562–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10856315

18. British guideline on the management of asthma Quick Reference Guide [Internet]. London; 2016 [cited 2018 Dec 14]. Available from: www.brit-thoracic.org.uk

19. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A Clinical Index to Define Risk of Asthma in Young Children with Recurrent Wheezing. Am J Respir Crit Care Med [Internet]. 2000 [cited 2019 Jan 23];162:1403–6. Available from: www.atsjournals.org

20. Reddel HK, Robin Taylor D, Bateman ED, Boulet L-P, Boushey HA, Busse WW, et al. American Thoracic Society Documents An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. Am J Respir Crit Care Med [Internet]. 2009 [cited 2018 Dec 19];180:55–99. Available from: www.atsjournals.org

21. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2018. Global Initiative for Asthma. 2018.

22. Boulet LP, Becker A, Bérubé D, Beveridge R, Ernst P. Canadian Asthma Consensus Report. CMAJ [Internet]. 1999 Nov 30 [cited 2018 Dec 15];161(11 Suppl):S1-61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10906907

23. Tønnesen P, Pisinger C, Hvidberg S, Wennike P, Bremann L, Westin Å, et al. Effects of smoking cessation and reduction in asthmatics. Nicotine Tob Res [Internet]. 2005 Feb 1 [cited 2018 Dec 18];7(1):139–48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15804686

24. Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP. Smoke-free Legislation and Hospitalizations for Childhood Asthma. N Engl J Med [Internet]. 2010 Sep 16 [cited 2018 Dec 18];363(12):1139–45. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1002861

25. Gøtzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. Allergy [Internet]. 2008 Jun 1 [cited 2018 Dec 27];63(6):646–59. Available from: http://doi.wiley.com/10.1111/j.1398-9995.2008.01690.x

26. Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, Buist AS, et al. Assessing

Future Need for Acute Care in Adult Asthmatics. Chest [Internet]. 2007 Oct [cited 2019 Jan 15];132(4):1151–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17573515

27. Hojas de recomendaciones | SEICAP - Profesionales [Internet]. [cited 2019 Jan 15]. Available from: http://www.seicap.es/es/hojas-de-recomendaciones_30445

28. American Thoracic Society Documents Guidelines for Assessing and Managing Asthma Risk at Work, School, and Recreation. Am J Respir Crit Care Med [Internet]. 2004 [cited 2018 Dec 28];169:873–81. Available from: http://www.

29. Plaza V, Serrano J, Picado C, Sanchis J, High Risk Asthma Research Group. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. Eur Respir J [Internet]. 2002 May 1 [cited 2018 Dec 18];19(5):846–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12030723

30. Lo P-C, Tsai Y-T, Lin S-K, Lai J-N. Risk of asthma exacerbation associated with nonsteroidal anti-inflammatory drugs in childhood asthma: A nationwide population-based cohort study in Taiwan. Medicine (Baltimore) [Internet]. 2016 Oct [cited 2018 Dec 26];95(41):e5109. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27741128

31. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J [Internet]. 1999 Oct 1 [cited 2018 Dec 17];14(4):902–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10573240

32. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol [Internet]. 2004 Jan 1 [cited 2019 Jan 3];113(1):59–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14713908

33. Meltzer EO, Busse WW, Wenzel SE, Belozeroff V, Weng HH, Feng J, et al. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. J Allergy Clin Immunol [Internet]. 2011 Jan 1 [cited 2018 Dec 16];127(1):167–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21093024

34. Plaza V, Cosio BG, Entrenas LM, Olaguíbel JM, Pérez de Llano L, Quirce S. Papel de la medición de la FE NO en el diagnóstico y control del asma. Debate del grupo multidisciplinar de expertos de la reunión Asma Meeting Point 2017. Arch Bronconeumol [Internet]. 2018 Apr 1 [cited 2019 Jan 23];54(4):237–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300289617304003

35. Asthma Exacerbation. J Investig Allergol Clin Immunol [Internet]. 2010 [cited 2018 Dec 16];20(1):27–30. Available from: http://www.jiaci.org/issues/vol20s1/7.pdf

36. Bousquet J, Bousquet PJ, Godard P, Daures J-P. The public health implications of asthma. Bull World Health Organ [Internet]. 2005 [cited 2018 Dec 29];83(7). Available from: www.who.int/

37. Bronchial asthma [Internet]. WHO. World Health Organization; 2010 [cited 2018 Dec 29]. Available from: https://www.who.int/mediacentre/factsheets/fs206/en/

38. Luczynska C, Tredwell E, Smeeton N, Burney P. A randomized controlled trial of mite allergen-impermeable bed covers in adult mite-sensitized asthmatics. [cited 2019 Jan 22]; Available from: https://pdfs.semanticscholar.org/7ef2/85d5da565a66451c19508d47d5075d0128bf.pdf

39. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Lynch MP, Kaczmarek JL, et al. Effectiveness of indoor allergen reduction in asthma management: A systematic review. J

Allergy Clin Immunol [Internet]. 2018 May 1 [cited 2018 Dec 29];141(5):1854–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29452202

40. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, et al. Results of a Home-Based Environmental Intervention among Urban Children with Asthma. N Engl J Med [Internet]. 2004 Sep 9 [cited 2019 Jan 22];351(11):1068–80. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa032097

41. Turcotte DA, Alker H, Chaves E, Gore R, Woskie S. Healthy homes: in-home environmental asthma intervention in a diverse urban community. Am J Public Health [Internet]. 2014 Apr [cited 2019 Jan 22];104(4):665–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24524511

42. Nurmagambetov TA, Barnett SBL, Jacob V, Chattopadhyay SK, Hopkins DP, Crocker DD, et al. Economic Value of Home-Based, Multi-Trigger, Multicomponent Interventions with an Environmental Focus for Reducing Asthma Morbidity. Am J Prev Med [Internet]. 2011 Aug 1 [cited 2019 Jan 23];41(2):S33–47. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0749379711003205

43. Maneechotesuwan K, Essilfie-Quaye S, Kharitonov SA, Adcock IM, Barnes PJ. Loss of Control of Asthma Following Inhaled Corticosteroid Withdrawal Is Associated With Increased Sputum Interleukin-8 and Neutrophils. Chest [Internet]. 2007 Jul [cited 2019 Jan 14];132(1):98–105. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17550933

44. Marrugat J. Calculadora de Grandària Mostral GRANMO v.7.12 [Internet]. Institut Municipal d'Investigació Mèdica. Barcelona; [cited 2019 Jan 10]. Available from: https://www.imim.cat/ofertadeserveis/software-public/granmo/

45. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a Standardized Version of the Asthma Quality of Life Questionnaire. Chest [Internet]. 1999 May 1 [cited 2019 Jan 3];115(5):1265–70. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0012369215352788

46. Artino AR, La Rochelle JS, Dezee KJ, Gehlbach H, Gehlbach H. Developing questionnaires for educational research: AMEE Guide No. 87. [Internet]. Vol. 36, Medical teacher. Informa Healthcare; 2014 [cited 2019 Jan 13]. 463-74 p. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24661014

47. Standardization of Spirometry, 1994 Update. [Internet]. Vol. 152, American Journal of Respiratory and Critical Care Medicine. 1995 [cited 2019 Jan 3]. 1107-1136 p. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7663792

48. Bandura A. Social foundations of thought and action. Englewood Cliffs, NJ: Prentice- Hall. 1986.

17 ANNEXES

17.1 ANNEX 1: ACQ :ASTHMA CONTROL QUESTIONNAIRE

Le rogamos responda a las preguntas de 1 a 6.
Marque la casilla correspondiente a la respuesta que mejor describa cómo se ha encontrado a lo largo de la última semana.

1. En promedio, durante la última semana, ¿con qué frecuencia se despertó por la noche debido al asma?

A. Nunca
B. Varias veces
C. Unas pocas veces
D. Casi nunca
E. Incapaz de dormir, debido al asma
F. Muchísimas veces
G. Muchas veces

2. En promedio, durante la última semana, ¿cómo fueron de graves los síntomas de asma que tuvo al despertarse por la mañana?

A. No tuvo síntomas
B. Síntomas moderados
C. Síntomas ligeros
D. Síntomas muy ligeros
E. Síntomas muy graves
F. Síntomas graves
G. Síntomas bastante graves

3. En general, durante la última semana, ¿hasta qué punto el asma le limitó en sus actividades?

A. Nada limitado
B. Moderadamente limitado
C. Poco limitado
D. Muy poco limitado
E. Totalmente limitado
F. Extremadamente limitado
G. Muy limitado

4. En general, durante la última semana, ¿hasta qué punto notó que le faltaba el aire debido al asma?

A. Nada en absoluto
B. Muy poco
C. Un poco

D. Moderadamente
E. Bastante
F. Mucho
G. Muchísimo

5. En general, durante la última semana, ¿cuánto tiempo tuvo silbidos o pitidos al respirar?

A. Nada en absoluto
B. Nunca
C. Casi nunca
D. Poco tiempo
E. Parte del tiempo
F. Casi siempre
G. Siempre

6. En promedio, durante la última semana, ¿cuántas inhalaciones de la medicación que usa para aliviar rápidamente los síntomas (Ventolin, Terbasmin o Buto-asma) utilizó al día?

A. Ninguna
B. 1 - 2 inhalaciones la mayoría de los días
C. 3 - 4 inhalaciones la mayoría de los días
D. 5 - 8 inhalaciones la mayoría de los días
E. 9 - 12 inhalaciones la mayoría de los días
F. 13 - 16 inhalaciones la mayoría de los días
G. Más de 16 inhalaciones la mayoría de los días

Si no está seguro de cómo responder a esta pregunta, le rogamos pida ayuda para hacerlo.

A rellenar por un empleado del centro sanitario
FEV1 pre-broncodilatador .....
FEV1 de referencia .....
%FEV1 del valor de referencia .....

Anote los valores reales en la línea de puntos y puntúe el %FEV1 del valor de referencia en la siguiente columna

A. 95% del valor de referencia
B. 95-90%
C. 89-80%
D. 79-70%
E. 69-60%
F. 59-50%
G. <50% del valor de referencia

17.2 ANNEX 2: ACT: ASTHMA CONTROL TEST

Este test sirve para valorar el control del asma. Marque con un círculo el valor de cada respuesta. Sume los cinco valores.

A. Durante las últimas **4 semanas**, ¿con qué frecuencia le impidió el **asma** llevar a cabo sus actividades en el trabajo, la escuela o el hogar?

1. Siempre
2. Casi siempre
3. Algunas veces
4. Pocas veces
5. Nunca

B. Durante las últimas **4 semanas**, ¿con qué frecuencia ha sentido que le faltaba el aire?

1. Más de una al día
2. Una vez al día
3. De tres a seis veces por semana
4. Una o dos veces por semana
5. Nunca

C. Durante las últimas **4 semanas**, ¿con qué frecuencia le despertaron por la noche o más temprano de lo habitual por la mañana los síntomas de **asma** (sibilancias/pitos, tos, falta de aire, opresión o dolor en el pecho)?

1. cuatro noches o más por semana
2. De dos a tres noches por semana
3. Una vez por semana
4. Una o dos veces
5. Nunca

D. Durante las últimas **4 semanas**, ¿con qué frecuencia ha utilizado su inhalador de rescate (por ejemplo, salbutamol, Ventolín, Terbasmín…)?

1. Tres veces o más al día
2. Una o dos veces al día
3. dos o tres veces por semana
4. Una vez por semana o menos
5. Nunca

E. ¿Cómo calificaría el control de su **asma** durante las últimas **4 semanas**?

1. Nada controlada
2. Mal controlada
3. Algo controlada
4. Bien controlada
5. Totalmente controlada

Resultado:

Total de 25: Control total del asma

De 20 a 24 : Buen control del asma

23 o menos: Asma no controlada

17.3 ANNEX 3: AQLQ: ASTHMA QUALITY-OF-LIFE QUESTIONNAIRE

EN GENERAL, ¿CON QUÉ FRECUENCIA **DURANTE LAS 2 ÚLTIMAS SEMANAS**:

	Siempre	Casi siempre	ran parte del tiempo	Parte del tiempo	Poco tiempo	Nunca
1. NOTÓ QUE LE FALTABA EL AIRE debido al asma?	1	2	3	4	5	7
2. Sintió que le molestaba el POLVO, o tuvo que evitar un lugar debido al POLVO?	1	2	3	4	5	7
3. Se sintió FRUSTRADO O IRRITADO debido al asma?	1	2	3	4	5	7
4. Sintió molestias debido a la TOS?	1	2	3	4	5	7
5. TUVO MIEDO DE NO TENER A MANO SU MEDICACIÓN PARA EL ASMA?	1	2	3	4	5	7
6. Notó una sensación de AHOGO U OPRESIÓN EN EL PECHO?	1	2	3	4	5	7
7. Sintió que le molestaba el HUMO DEL TABACO, o tuvo que evitar un lugar debido al HUMO DEL TABACO?	1	2	3	4	5	7
8. Tuvo DIFICULTADES PARA DORMIR BIEN POR LA NOCHE debido al asma?	1	2	3	4	5	7

EN GENERAL, ¿CON QUÉ FRECUENCIA **DURANTE LAS 2 ÚLTIMAS SEMANAS**:

	Siempre	Casi siempre	ran parte del tiempo	Parte del tiempo	Poco tiempo	Nunca
9. Se sintió PREOCUPADO POR	1	2	3	4	5	7
10. Sintió SILBIDOS O PITOS en	1	2	3	4	5	7
11. Sintió que le molestaba o tuvo que evitar salir de casa debido AL TIEMPO O A LA CONTAMINACIÓN ATMOSFÉRICA?	1	2	3	4	5	7

¿HASTA QUÉ PUNTO EL ASMA LE HA LIMITADO **PARA HACER ESTAS ACTIVIDADES** DURANTE LAS 2 ÚLTIMAS SEMANAS?

	Totalmente limitado	Extremada-mente limitado	Muy limitado	Moderada-mente limitado	Algo limitado	Poco limitado	Nada limitado
12. ESFUERZOS INTENSOS (como darse prisa, hacer ejercicio, subir escaleras corriendo, hacer deporte)	1	2	3	4	5	6	7
13. ESFUERZOS MODERADOS (como caminar, hacer las tareas del hogar, trabajar en el jardín o en el huerto, hacer la compra, subir escaleras sin correr)	1	2	3	4	5	6	7

¿HASTA QUÉ PUNTO EL ASMA LE HA LIMITADO **PARA HACER ESTAS ACTIVIDADES** DURANTE LAS 2 ÚLTIMAS SEMANAS?

	Totalmente limitado	Extremada-mente limitado	Muy limitado	Moderada-mente limitado	Algo limitado	Poco limitado	Nada limitado
14. ACTIVIDADES SOCIALES (como hablar, jugar con niños/animales domésticos, visitar a amigos/familiares)	1	2	3	4	5	6	7
15. ACTIVIDADES RELACIONADAS CON SU TRABAJO (tareas que tiene que hacer en su trabajo*)	1	2	3	4	5	6	7

** Si no está trabajando, responda a esta pregunta pensando en las tareas que tiene que hacer la mayoría de los días.*

CLAVE DE LAS DIMENSIONES:

Síntomas: 1, 4, 6, 8, 10
Limitación de actividades: 12, 13, 14, 15
Función emocional: 3, 5, 9
Estímulos ambientales: 2, 7, 11

17.4 ANNEX 4: TAI: TEST OF ADHERENCE TO INHALERS

1. En los últimos 7 días ¿cuántas veces olvidó tomar sus inhaladores habituales?
☐ 1. Todas ☐ 2. Más de la mitad ☐ 3. Aprox.la mitad ☐ 4. Menos de la mitad ☐ 5. Ninguna

2. Se olvida de tomar los inhaladores:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

3. Cuando se encuentra bien de su enfermedad, deja de tomar sus inhaladores:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

4. Cuando está de vacaciones o de fin de semana, deja de tomar sus inhaladores:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

5. Cuando está nervioso/a o triste, deja de tomar sus inhaladores:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

6. Deja de tomar sus inhaladores por miedo a posibles efectos secundarios:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

7. Deja de tomar sus inhaladores por considerar que son de poca ayuda para tratar su enfermedad:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

8. Toma menos inhaladores de las que su médico le prescribió:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

9. Deja de tomar sus inhaladores porque considera que interfieren con su vida cotidiana o laboral:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

10. Deja de tomar sus inhaladores porque tiene dificultad para pagarlos:
☐ 1. Siempre ☐ 2. Casi siempre ☐ 3. A veces ☐ 4. Casi nunca ☐ 5. Nunca

TAI 12 ítems. Orientación del patrón de incumplimiento

Las dos siguientes preguntas las deberá responder el profesional sanitario responsable del paciente según los datos que figuran en su histórico clínico (pregunta 11) y tras comprobar su técnica de inhalación (pregunta 12).

11.¿Conoce o recuerda el paciente la pauta (dosis y frecuencia) que se le prescribió?
☐ 1. No ☐ 2. Sí

12.La técnica de inhalación del dispositivo del paciente es:
☐ 1. Con errores críticos ☐ 2. Sin errores críticos o correcta

Puntuación 11-12 ítems

17.5 ANNEX 5: PRELIMINARY QUESTIONNAIRE

1. ¿Está expuesto al humo del tabaco de otras personas? Si ☐ No ☐
2. ¿Está expuesto al humo de la estufa de la leña, chimenea o estufa de gas? Si ☐ No ☐
3. ¿Está en contacto, donde vive (vivienda habitual u otra), con elementos en los cuales se puede acumular polvo (cortinas, muebles tapizados, alfombras…)? Si ☐ No ☐
4. ¿Está en contacto, donde trabaja, con elementos en los cuales se acumulan polvo (archivos, biblioteca, almacenaje…)? Si ☐ No ☐
5. ¿Nota cualquier tipo de síntoma (estornudos, picor nasal, mucosidad, pitos, ahogo…) en contacto con el polvo? Si ☐ No ☐
6. ¿Utiliza, aunque sea ocasionalmente, productos de limpieza (amoniaco, lejía, desengrasantes…) o ambientadores? Si ☐ No ☐
7. ¿Utiliza, aunque sea ocasionalmente, productos de higiene personal como desodorantes, perfumes, colonias, etc.? Si ☐ No ☐
8. ¿Está en contacto, donde vive o trabaja, con manchas de humedad o nota olor de humedad? Si ☐ No ☐
9. ¿Tiene contacto con animales domésticos de pelo o pluma? Si ☐ No ☐
10. ¿Toma, aunque sea ocasionalmente, medicamentos antiinflamatorios o para el dolor (aspirina, ibuprofeno, diclofenaco, metamizol, naproxeno…)? Si ☐ No ☐
11. ¿En qué trabaja? _____
12. ¿Está en contacto donde trabaja o en su tiempo libre con humos, gases o aerosoles, pinturas, barnices o colas? Si ☐ No ☐
13. ¿Considera usted que hay algún otro elemento que empeora su sintomatología nasal o respiratoria? Si ☐ No ☐

En caso afirmativo ¿Cuál? _____

17.6 ANNEX 6: INTERVENTION

Intervention to avoid pro-inflammatory agents

It is important to highlight that these measures will be adjusted to the IgE profile and the results from the questionnaire.

The recommendations are *based on Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica.* (27)

HOUSE DUST MITE

House dust mite are microscopic microorganisms, that live in dust, pillows, mattresses and stuffed toys. The most frequent species are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. The perfect conditions for house dust mite to grow are a humidity of more than 50% and warmth. To reduce them, a strategy can be undertaken. This strategy includes education about this microorganism and different measures like:

- Removal of upholstered furniture.
- Avoidance of humidifiers. Air conditioning and heating can be useful as they keep the humidity <50%.
- Removal of different objects that can accumulate dust like stuffed toys and carpets.
- If possible, use of vacuum cleaners with a High Efficiency Particulate Air (HEPA) filter.
- Washing bedding once per week and drying it in a heated drier

PETS

Dogs and cats are the most frequent pets, but there are also other animals like hamsters and birds. It is one of the most frequent allergies. The allergens take months to disappear and are wide spread.

The best way to reduce allergens is to remove the pet, but very often it cannot be done, other recommendations are:

- Keeping the animal outside the house, preventing it from entering the patient´s bedroom.
- Aggressive cleaning of furniture, walls and carpet.
- Keeping the animal clean. Washing it twice a week preferably.

- Use of vacuum with HEPA filter.
- Removal of upholstered furniture.

MOLD

Mold comprehend hundreds of species of saprophytic fungi. The perfect conditions for mold to grow are a humidity of more than 50% and warmth

The recommendations are:

- Localization of mold contaminated items and remove them.
- Reparation of leaks and utilization of anti-mold paint.
- Avoidance of gardening and interior plants.
- Airing the rooms.
- Aggressive cleaning of moist areas.
- Exposure of the room to sunlight.
- Keeping the first minutes the windows open, when air conditioning is used in the house or in the car.
- Avoidance of humidifiers.
- Installation of air extractors in the toilets and moist areas.

POLLEN

The recommendations are:

- Maintenance of closed windows in the car and in the house.
- Bathing and changing clothes after a trip to remove allergens from hair and body.
- Not hanging the clothes outside.
- Avoidance of trips on windy days with a high concentration of pollen. Information about pollen concentration can be found in www.pollenes.com
- Utilization of anti-pollen filters in humidifiers and air conditioning.
- Avoidance of gardening.
- Masks can be beneficial, on days with a high concentration of pollen.

WORK ALLERGENS-IRRITANTS

There are more than 300 products that act as an allergen or as an irritant, if the patient is in contact with one of these products, measures to avoid them are recommended.

Impact of an intervention on proinflammatory agents in asthmatic patients

The best way to reduce harm is the cessation of the exposure, this can be achieved by changing jobs or modifying the irritant to another non-harmful. But very often it cannot be done so other interventions should be implemented:

- Utilization of masks and a correct ventilation of the room.
- Chemical must be kept closed.
- Avoidance of mixing the chemicals.

PASSIVE SMOKING

The recommendations are:

- Avoid being with a person while he/she is smoking.
- The person who smokes should smoke outside the house.

NSAID AVOIDANCE

The recommendation is to avoid NSAID like:

- Salicylic acid and derivates (Aspirina ®)
- Acetic acid derivates (Indopyrrole): Indometacina
- Derived from propionic acid.: Ibuprofen, Dexketoprofene or enantyum®, Naproxene or antalgin®.
- Derivatives of aryl acetic acid: Diclofenac or voltaren®.
- Pyrazolones: Metamizol or nolotil®.

Whenever analgesic medication is needed, we recommend the use of paracetamol.
If it is not possible, the use of selective COX2 inhibitors is recommended such as: Meloxicam, celecoxib (celebrex® and artilog®) or etoricoxib (arcoxia®).

17.7 ANNEX 7: INFORMED SHEET FOR PARTICIPANTS

HOJA DE INFORMACIÓN SOBRE EL ENSAYO CLÍNICO

Título del estudio: Impacto de una intervención sobre agentes proinflamatorios en pacientes asmáticos.

Investigadores: _____

Centro: _____

Nos dirigimos a usted para informarle sobre la realización de un estudio de investigación en el que se le invita a participar. El presente estudio ha sido aprobado por el Comité de Ética e Investigación Clínica (CEIC) del Hospital Josep Trueta.

Nuestra intención es que usted reciba la información de forma correcta y que esta sea suficiente para que pueda decidir si quiere participar o no en este estudio. Por este motivo, le agradeceríamos que leyera atentamente esta hoja informativa y posteriormente nosotros le aclararemos las dudas que le puedan surgir.

Primeramente, debe de saber que la participación en este estudio es de forma completamente VOLUNTARIA. Si decidir participar en el estudio debe saber que podrá abandonarlo en cualquier momento sin que esto suponga una alteración de la relación con su médico/medica ni que se produzca ningún perjuicio en su tratamiento.

Finalidad: Nuestro objetivo es conocer si una intervención donde el paciente recibe el tratamiento habitual y medidas para evitar agentes irritantes y alérgenos específicos del paciente resultan más eficaces que el propio tratamiento habitual por sí solo.

Descripción del proceso: Durante su participación en el estudio le informaremos sobre los objetivos del protocolo y resolveremos las dudas que le puedan surgir durante el proceso.

Actualmente, todos los pacientes que hayan tenido una exacerbación del asma en el último año y acudan a la visita se les invitará a participar en el estudio voluntariamente.

En la primera visita programada a la consulta, se le solicitará que nos facilite información personal y familiar que resulte de interés para concluir si usted presenta los requisitos para participar en el estudio. En caso afirmativo, si firma el consentimiento informado, se le propondrá realizar una serie de pruebas y cuestionarios: 1) Test del Control del Asma, 2) Cuestionario de Calidad de Vida en Pacientes con Asma, 3) Espirometría, 4) Analítica (IgE total e IgE específica) y 5) Examen de Óxido Nítrico Espirado.

Más tarde, todos los pacientes serán asignados de forma aleatoria mediante un sistema informático a una de las dos intervenciones.

Si usted pertenece al nuevo enfoque, se le realizará un cuestionario sobre alérgenos e irritantes y según los resultados obtenidos en las pruebas y en el cuestionario, se propondrán medidas de evitación de los alérgenos e irritantes a los cuales es usted sensible. Adicionalmente, se realizarán medidas para mejorar la adherencia al tratamiento basal. En el otro grupo, únicamente se realizarán medidas para mejorar la adherencia al tratamiento basal.

Controles del estudio: Al mes y a los 6 meses, se realizarán controles para valorar y mejorar la adherencia a las nuevas medidas y al tratamiento basal y al otro grupo, únicamente medidas para mejorar la adherencia al tratamiento basal. Además, es importante destacar que existe un número de teléfono disponible para cualquier duda e incidencia que surja a lo largo del proceso.

Beneficios y riesgos: Si usted está en el grupo experimental se puede beneficiar de mejores resultados para el asma con menos riesgos de complicaciones, pero tendrá que someterse a ciertas medidas. Si usted recibe solamente el tratamiento convencional, recibirá el mismo tratamiento que si no participase en el estudio. También es posible que usted no obtenga ningún beneficio directo por participar en el estudio; no obstante, se prevé que la información que se obtenga pueda beneficiar en un futuro a otros pacientes y pueda contribuir a un mejor conocimiento del efecto de los alérgenos e irritantes para el asma.
No se prevén riesgos ni inconvenientes por participar en este estudio.
Los participantes no recibirán una compensación económica por participar en el ensayo clínico, pues sesgaría la selección de los pacientes.

Seguro y responsabilidades: El promotor del estudio dispone de una póliza de seguro que se ajusta a la legislación vigente y que le proporcionará la compensación e indemnización en caso de menoscabo de su salud o de lesiones que puedan producirse en relación con su participación en el estudio

Confidencialidad: Su información médica y aquella obtenida sobre usted derivada de este estudio será codificada y archivada confidencialmente de acuerdo con la *Ley Orgánica 15/1999 sobre la Protección Personal de Datos* y el correspondiente *RD 1720/2007* y no podrá ser hecha pública.

El acceso a su información personal quedará restringido al personal del estudio, autoridades sanitarias (AEMPS) y CEIC cuando lo consideren oportuno siempre y cuando sea respetada la legislación vigente.

17.8 ANNEX 8: INFORMED CONSENT

CONSENTIMIENTO INFORMADO

Título del estudio: Impacto de una intervención sobre agentes proinflamatorios en pacientes asmáticos.

Yo, Sr/Sra. _____ con DNI _____ declaro que:

He leído y comprendo la hoja informativa sobre el estudio que se me ha entregado.

- He podido hacer las preguntas necesarias respecto al estudio.
- He sido informado/a de las implicaciones y objetivos del estudio.
- Entiendo que mi participación es voluntaria y no remunerada.
- Entiendo que se respetara la confidencialidad de mis datos.
- Entiendo que puedo revocar el consentimiento sin necesidad de justificación y sin que conlleve modificación de mi asistencia sanitaria.

Conforme a lo anteriormente mencionado, acepto voluntariamente participar en este estudio.

Doy permiso para que la información resultante de este estudio sea utilizada en futuras investigaciones relacionadas con esta patología.

En Girona, a _____ de _____ de 20

Firma del paciente:	Firma del investigador:

17.9 Annex 9: Data Collection Sheet

CASE REPORT FORM	Centro:
Project title: Impact of an intervention on proinflammatory agents in asthmatic patients.	Patient code:

INSTRUCTIONS:

- All the questions should be answered.
- Do not leave any question unanswered. If the answer to a question is unknown, write "**NK**" (Not Known). If a requested test has not been done, write "**ND**" (Not Done).
- Where a choice is requested, **cross (X)** the appropriate response.

Patient has read the Information Sheet ☐

Patient has signed the Informed Consent ☐

PARTICIPANT INFORMATION

Date of birth: _____ Gender:

Cigarette Smoking:

- Non Smoker ☐
- Ex – Smoker ☐
- Active smoker ☐

- Male ☐
- Female ☐

Basal corticosteroide treatment:

- Low dose (<400mcg) ☐
- Middle dose (400-800mcg) ☐
- High dose (>800mcg) ☐

TESTS	Before	After
- AQLQ score	_____	_____
- ACT score	_____	_____
- TAI	_____	_____

SPIROMETRY Punctuation Before After

Pre-FEV1 _____ _____

Pos-FEV1 _____ _____

eNO Punctuation Before After

_____ // _____

QUESTIONNAIRE RESULTS

Mold ☐ Passive smoking ☐ Irritants ☐ Dust ☐ NSAID ☐

Animals ☐

IgE Before After

- Total IgE→_____ // _____
- High IgE for:

	Before	After
○ Cat dander	☐	☐
○ Dog dander	☐	☐
○ *Dermatophagoides farine*	☐	☐
○ *Dermatophagoides pteronyssinus*	☐	☐
○ *Alternaria alternata*	☐	☐
○ *Aspergillus niger*	☐	☐
○ *Aspergillus fumigatus*	☐	☐
○ *Cupressus arizonica*	☐	☐
○ *Cupressus sempervivens*	☐	☐
○ *Platanus acerifolia*	☐	☐
○ *Olea europea*	☐	☐
○ *Parietaria judaica*	☐	☐
○ *Parietaria officinalis*	☐	☐
○ *Plantago laceolata*	☐	☐
○ *Artemisa vulgaris*	☐	☐
○ *Secale cereale*	☐	☐

FOLLOW UP INFORMATION

- Time to the first severe exacerbation _____ DAYS
- Time to the first moderate exacerbation _____ DAYS
- Number of times of reliever medication used _____
- Number of moderate exacerbations _____
- Number of severe exacerbations _____