ERS/EAACI statement on adherence to international adult asthma guidelines

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Abstract: (200 words)

Guidelines aim to standardize and optimize asthma diagnosis and management. Nevertheless, adherence to guidelines is suboptimal and may vary across different healthcare professional (HCP) groups.

Further to these concerns, this ERS/EAACI Statement aims (1) via an international online survey, to evaluate the understanding of and adherence to international asthma guidelines by HCPs of different specialties, (2) via systematic reviews, to assess strategies focused at improving implementation of guideline-recommended interventions, and compare process and clinical outcomes in patients managed by HCP of different specialties.

The online survey identified discrepancies between HCPs of different specialties which may be due to poor dissemination or lack of knowledge of the guidelines but also a reflection of the adaptations made in different clinical settings, based on available resources. The systematic reviews demonstrated that multifaceted quality improvement initiatives addressing multiple challenges to guidelines adherence are most effective in improving guidelines adherence. Differences in outcomes between patients managed by Generalists or Specialists should be further evaluated.

Guidelines need to consider the heterogeneity of real-life settings for asthma management and tailor their recommendations accordingly. Continuous, multifaceted quality improvement processes are required to optimize and maintain guidelines adherence. Validated referral pathways for uncontrolled asthma or uncertain diagnosis are needed.

Take home message: @EuroRespSoc @AllergyEAACI Statement: Guidelines need to account for differences in resource availability across various asthma care settings. Continuous, multifaceted quality improvement processes are needed to optimize and maintain guidelines adherence.

INTRODUCTION

In the European Union, over 20 million people suffer from asthma[1]. During the 1990s there was a rapid decrease in asthma mortality[2], probably related to the increased use of inhaled corticosteroids (ICS)[3]. However, during the last decade, asthma mortality rates have plateaued, and a consistently high proportion of patients have uncontrolled asthma[4,5]. As a result, many patients with asthma still have impaired quality of life and suffer from chronic respiratory symptoms, often including night-time symptoms, causing sleep disturbance, excessive daytime sleepiness and decreased work productivity[6,7].

The reason for this lack of improvement in achieving asthma control is multifactorial. Asthma is a chronic inflammatory airway disease needing regular long-term anti-inflammatory treatment for symptom control and prevention of acute attacks and/or lung function decline. ICS are the mainstay of asthma medication, but many patients do not adhere to regular treatment[8] with overreliance on short acting beta-agonists (SABAs), leading to under-treatment of the chronic inflammation[9]. Another possible explanation is the heterogeneity of asthma, so that subgroups of patients require different interventions, according to a personalized approach based on asthma phenotypes[10]. A proportion have severe asthma[11] and need to be identified and offered specific regimes such as biological treatment with anti-IgE, anti-IL5 or anti-IL4/IL13[12,13]. Other factors such as poor inhaler adherence and technique, lack of self-management support, exposure to triggers, unavoidable environmental factors, limited accessibility to diagnostic facilities and medication, could also contribute[14,15,16].

Clinical practice guidelines, based on available evidence, define disease control and risk of acute attacks and make recommendations to standardise and optimise asthma diagnosis and management. National and international asthma guidelines have been available since the 1990s and are continuously being updated[11,17,18]. However, there are concerns that adherence to guidelines is far from optimal and varies between different groups of healthcare professionals (HCPs)[19,20]. In addition, the 'one-size-fits-all' approach of guidelines (typically based on efficacy in highly selected populations evaluated in randomised controlled trials) limits perceived applicability and relevance in real-life practice[21]. Further to these concerns, we aimed (1) to evaluate and compare the understanding of and adherence to international asthma guidelines by HCPs of different specialties, (2) to assess effectiveness of strategies aimed at improving implementation of guideline-recommended interventions, and (3) to compare process and clinical outcomes in patients managed by Specialists (respiratory physicians or allergists) or Generalists (internists or general practitioners).

METHODS

This task force was formed by the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in 2015 and was chaired by two representatives from the ERS (AGM and CJ) and two from EAACI (OT and IA) who were responsible for project management and co-ordination. The task force was composed of experts from three ERS Assemblies (1- Respiratory clinical care and physiology, 5- Airway Diseases: asthma, COPD and chronic cough, and 6- Epidemiology and Environment), from four EAACI bodies (Asthma Section, Primary Care Interest Group, Executive Committee and Junior Members Assembly) and from the International Primary Care Respiratory Group (IPCRG) (JCS). It involved experts in respiratory medicine and science, allergy and general practice, and also a lay person with lived experience of asthma (BF). The co-chairs met in January 2017 and September 2018 and a face-to-face meetings of the task force was held in January 2019, with teleconferences and e-mail correspondence as required. All task force members signed conflict-of-interest statements at the beginning of the project and updated them at project finalisation or when any new relevant conflict appeared, in line with the ERS and EAACI procedures. This report was informed by an international online survey (Aim 1) and two systematic reviews (Aims 2 and 3).

On-line survey (Aim 1)

Three online questionnaires pertaining to different clinical cases were prepared by the panel and uploaded to the SurveyMonkey platform (available in the online supplement). The cases were not related to a specific clinical setting so that the questionnaires were applicable to all specialties targeted by the survey. The first scenario was a mild type 2 (T2) asthma, the second a severe T2 asthma, and the third a severe non-T2 asthma. T2 asthma is defined by the presence of eosinophilic inflammation driven via three pathways: IgE, IL-5 or IL-4/IL-13[22]. Allergic asthma is a sub-endotype of T2 asthma, frequently with childhood onset and associated with other atopic diseases (allergic rhinitis, atopic dermatitis, food allergy). Another sub-endotype is non-allergic eosinophilic asthma, with adult-onset, usually more difficult to control[22]. Non-T2 asthma is usually defined by the lack of eosinophilic inflammation[22]. Its mechanisms are less well described as opposed to T2 asthma[22].

Introductory questions collected participants' age, gender, specialty, level of training (trained or in training), and clinical setting. The T2 asthma questionnaires were sent out in May 2018 as a pair (mild T2 questions were completed prior to the severe T2 questions), and the non-T2 questionnaire was distributed in August 2018. Surveys were open for approximately 6 weeks. For most of the questions more than one answer could be chosen. Participants of the second survey were not asked if they had

also taken part in the first survey. After completion, a participant could not take the survey again on the same computer.

Both survey links were disseminated via mass emails with links to the online surveys, to relevant members of the participating organisations (EAACI: Asthma Section, ENT Section, Immunotherapy, Occupational Allergy, Allied Health and Primary Care Interest Groups, EAACI National Societies platform; ERS aforementioned assemblies; IPCRG). EAACI and ERS social media platforms supplemented the dissemination of the survey links.

Survey results were analysed based on the participants' specialty. Specialties were grouped into three main categories: i) 'Allergy Doctor' if participant indicated they were Allergy-Asthma Specialist, Allergy Specialist or Allergy Trainee, ii) 'Respiratory Doctor' if participant indicated they were an Asthma Specialist, Respiratory Doctor or Respiratory Medicine Trainee, iii) 'Generalist' if participant indicated they were General Practitioner, General Practitioner Trainee, Internist, Internal Medicine Trainee, Specialist Nurse or Nurse Trainee.

The results of the questionnaire answers are presented as % affirmative answers. Comparisons between the three groups were made using Chi-squared test. Stata 15 (Stata Corp, College Station, Texas USA) was used for the calculations.

Ethics approval was not necessary for this survey, as no personally identifiable data were collected.

Systematic review methods (Aims 2 and 3)

Two systematic reviews (SRs) were conducted to evaluate (Aim 2) the effectiveness of strategies to improve adherence to guidelines on the diagnosis, assessment and long-term/acute treatment of asthma, including maintenance and acute attacks management, and (Aim 3) the process and clinical outcomes in patients managed by Specialists (respiratory physicians or allergists) compared to Generalists (internists or general practitioners) (Table 1). The SRs followed Cochrane methodology[23]. Medline/PubMed was searched for studies published after 1990 (publication of the first asthma guideline[24]), using a search strategy that included controlled vocabulary and free search terms (available in the online supplement), to identify relevant studies. Reference lists of included studies and of any previous, relevant SRs were screened. Studies of any design addressing the two review questions were eligible if they assessed process outcomes (e.g. adherence to guideline recommendations) and/or asthma-related clinical outcomes. Two reviewers independently evaluated all identified abstracts for eligibility. The full texts of all potentially eligible manuscripts were similarly evaluated for inclusion by two reviewers. Disagreements were resolved by discussion between

reviewers. We extracted relevant data on study characteristics, process and clinical outcomes in a structured excel sheet. We evaluated methodological quality using the Cochrane Risk of Bias tool for randomised controlled trials (RCTs)[25] and the Risk Of Bias In Non-randomised Studies of interventions (ROBINS-I) for non-randomised studies[26].

As anticipated, we were not able to conduct meta-analyses, due to the significant methodological and clinical diversity, statistical heterogeneity, inconsistency, and incompleteness of outcomes reported in the included studies. Instead, we used narrative synthesis and present pertinent results of the included studies in a tabulated format. Findings are presented visually as harvest plots, which summarise the direction and significance of the effect on process and clinical outcomes for each of the studies along with information about study design, study population and methodological quality.[27,28]. To interpret the overall findings, we prioritised differences in clinical outcomes over process outcomes.

RESULTS

Survey results (Aim 1)

Survey 1: Mild T2 asthma and Severe T2 asthma

Of the 784 participants who started the mild T2 questionnaire, 507 also started the severe T2 asthma questions. The majority (70.8%) of the participants (n=784) were Respiratory Doctors as opposed to 18.5% and 10.7% who were Allergy Doctors and Generalists, respectively. The participants' speciality and categorisation for the sub-group analysis are summarised in Table 2. Most (45.2%) were tertiary care Specialists, 32.6% and 22.2% worked in secondary or primary care respectively.

Mild T2 asthma

Box 1.

Case vignette 1.

A 22-year-old female, non-smoker, maths student attends for a consultation in October complaining about occasional chest tightness and cough (especially when playing tennis), during late spring to mid-summer the last 4 years. She has never used any inhalers for her chest symptoms. Regular chest auscultation provides you with normal lung sounds.

She also mentions that during the same months she has been experiencing watery eyes and nose, nasal congestion as well as sneezing. These symptoms began early at adolescence and have been managed with as needed, over the counter antihistamines. She was diagnosed with eczema and egg allergy as a toddler with both conditions having resolved by the age of 10 years, which was the age she was last evaluated in an allergy clinic. She has a cat at home.

Additional information

Chest auscultation with fierce exhalation provides normal sounds. You had the possibility of performing spirometry and received the following outcomes: baseline spirometry resulted in FEV1/FVC ratio 0.75 and administration of 400 mcg salbutamol increased FEV1 by 10% (150 ml). What is your diagnosis and how would you manage the patient?

Follow-up

The patient comes back during the pollen season. She reports episodes of chest tightness and cough especially early in the morning when she is walking to work through a park and if walking back home late evening. She additionally mentions wakening up at night due to chest tightness and nasal blockage. She has been avoiding playing tennis because of these symptoms. She is receiving her antihistamine daily but no nasal spray. Regular chest auscultation provides you with normal lung sounds. Spirometry with reversibility results in 13% (220 ml) increase in FEV1 post the bronchodilator administration.

Responses about preferred diagnostic procedures are presented in Table 3. Spirometry with reversibility was the preferred diagnostic test in all groups. Home serial peak flow measurements were significantly more popular amongst the Generalists than the other groups and a third of the Respiratory Doctors would undertake bronchial provocation at the initial consultation compared to a

fifth of the other two groups. Of note, auscultation of the chest during forced expiration was seen as helpful by less than half of the Respiratory Doctors and Generalists. Statistically significant differences between the three groups were noted for the measurement of the fractional exhaled nitric oxide (FeNO), blood eosinophils, total serum IgE, skin prick test, specific IgE, and chest X-ray.

The mild T2 patient had normal spirometry and no bronchodilator reversibility when examined in autumn. The majority of the participants agreed that this did not exclude asthma as the patient was asymptomatic at the time. However, approximately 20% of the Allergy Doctors and 15% of the Respiratory and the Generalists were 'certain' about the diagnosis and would prescribe a reliever for use when needed (Table e1) [Note, this questionnaire was sent out in 2018, before the change in GINA guidelines recommending the maintenance and reliever therapy (MART) approach for mild asthma].

The majority of the participants across all groups agreed that the patient's asthma was uncontrolled (as per GINA classification)[17] when asthma status was reviewed during spring. Approximately 80% of the Allergy Doctors as opposed to 61.7% and 56.0% of the Respiratory and the Generalists respectively replied that the patient's phenotype was 'allergic asthma' ($p<0.0001$). As part of the same question, 30% of the Allergy Doctors (additionally) included the patient under 'T2 asthma' compared to 13.6% and 1.3% of the Respiratory and the Generalists ($p<0.0001$) (Table e1).

The majority of participants in all groups indicated that in addition to treatment for nasal symptoms, they would prescribe inhaled steroids and provide an asthma action plan. All asthma treatment options were similarly popular in the three groups except that half of the Allergy Doctors would commence the patient on allergen immunotherapy compared to 6.7% and 2.7% in the other groups ($p<0.0001$) (Table e4).

Severe T2 asthma:

Box 2.

Case vignette 2.

A 21 year-old male, BMI=23, comes for a consultation due to coughing, shortness of breath and wheezing. He has been suffering with asthma since childhood; from 3-12 years of age he was treated with inhaled budesonide, later on with fluticasone/salmeterol 50/250 dry powder inhaler, 1 puff twice-daily, while the last 4 years with fluticasone/salmeterol 50/500 dry powder inhaler, 1 puff twice-daily. Despite this treatment, he suffers from night symptoms twice a week which prompt him to use salbutamol. Playing football or cycling also cause asthma exacerbation especially during Spring. He complains of itchy eyes and nose, sneezing and runny nose all year round but worse during springtime. He uses loratadine on demand for his nasal and ocular symptoms.

He is a student in journalism, with no exposure to chemicals or other substances and doesn´t smoke. He lives in a house with a tree-garden in a small town, and does not keep pets.

In the patient with severe T2 asthma, spirometry with reversibility, FeNO, blood eosinophils, total IgE, skin prick test, specific IgE, and chest X-Ray were all statistically less popular among the Generalists than Specialists (Table 3).

The majority of participants agreed that the patient's asthma was uncontrolled (as per GINA Guidelines). Just 66% of the Generalists versus 91.9% of the Allergy and 76.4% of the Respiratory Doctors would evaluate the presence of comorbidities in order to manage this patient ($p<0.0001$). More than 80% of participants across all groups would evaluate patient's adherence and inhaler technique (Table e2).

Significantly more Allergy doctors regarded the patient's asthma type as 'allergic asthma' (71.7%) and/or T2 asthma (31.3%) than the other groups ($p=0.007$). Interestingly, a fifth of Generalists and one in ten Respiratory Doctors stated that they did not know the patient's asthma type ($p=0.001$). There was widespread agreement that the patient was at risk of acute attacks (Table e2).

Although only around two thirds of participants recognised uncontrolled rhinitis as a risk factor for asthma attacks, rhinitis treatment was the most popular option for asthma management, followed by montelukast. Significant differences were noted in terms of the third most popular treatment choice

which was tiotropium for the Respiratory Doctors (46.5%, p<0.0001) and allergen immunotherapy for the Allergy Doctors. (50.5%, p<0.0001) (Table e2).

The majority of participants would proceed with an asthma control test and/or a lung function with reversibility test at the patient's follow-up appointment. Fewer (53.2%) Generalists would use FeNO to investigate asthma control compared to Allergy (73.7%) and Respiratory Doctors (69.5%) (p=0.04). If asthma control was not achieved, 40% of Generalists would refer the patient to an asthma clinic while most of the Allergy and Respiratory Doctors would start the patient on omalizumab (Table e2).

Survey 2: Non T2 asthma

Box 3.

Case vignette 3.

A 50 year-old lady attends as an emergency due to breathlessness. She reports that her dyspnea has worsened over the last two weeks despite using 2 puffs of beclomethasone dipropionate/formoterol (100/6 μg) twice daily and that she now needs to use her reliever (salbutamol) four times a day. On presentation, she talks in phrases but wheezes, her oxygen saturation is 92%, pulse rate at 118bpm, respiratory rate at 28bpm, FEV1 72% pred., FVC 82% pred., FEV1/FVC 0.68 while electrocardiography is unremarkable. She was diagnosed with asthma 10 years ago (PC20 for methacholine <4 mg/ml), skin prick testing to common aeroallergens was negative. Since then she has been on high doses of inhaled corticosteroids but often uses salbutamol after exercise and sometimes during the night. She has to take oral corticosteroids around 4 times a year for asthma exacerbations and was hospitalized due to asthma twice in the last 5 years (once at ICU). She is 160 cm tall, weighs 90 kg, works in a dye-factory and has been occasionally smoking the last 30 years.

Follow-up information:

- Spirometry results are as following: FEV1 79% pred., FVC 82% pred., FEV1/FVC 0.72, reversibility 7% (150ml). Chest auscultation normal. She still needs to use her reliever at least three times a week.
- FeNO is 6 ppb. Skin prick testing with common aeroallergens is negative. Blood eosinophils 48/cml.

The majority (49.9%) of the 677 participants were Respiratory Doctors as opposed to 30.3% and 19.8% who were Allergy Doctors and Generalists respectively (Table 2). Most (45%) worked in tertiary care, while approximately 26% and 29% were working in secondary and primary care, respectively.

Deciding on emergency management was challenging for all groups and there were statistically significant differences in how much prednisolone should be prescribed (Table e3). At follow-up, the priority for all groups was to ensure that inhaler technique was correct. Of note, less than two-thirds of the participants across all groups considered evaluating for occupational exposure in this patient who worked in a dye factory (Table 3).

The majority of the participants agreed that the patient's asthma was uncontrolled and most considered that the patient's asthma phenotype was obesity-related (p=0.006) while a significantly higher percentage (19%) of the Respiratory Doctors classified the patient's asthma as T2 compared to the other specialties (p=0.002). Tiotropium (p=0.02) and education (p=0.96) were the most popular answers regarding the loptimal ong-term management of this patient. Allergy Doctors were more likely to consider anti-IL5 (p<0.0001) or anti-IgE (p=0.008) treatment (Table e3).

Fewer Generalists prioritized the assessment of comorbidities (p=0.049), adherence (p=0.01) and inhalation technique (p=0.05) compared to the other two groups. Smoking cessation was prioritised by all groups but pulmonary rehabilitation was chosen more often by Respiratory and Generalists than Allergy Doctors (Table e3).

Systematic review results (Aims 2 and 3)

Details of the search and selection process are summarised in a PRISMA flowchart (figure 1). Our search yielded 3,722 unique titles, of which 52 studies evaluated strategies aimed at improving adherence to guidelines on diagnosis, assessment and/or long-term management of asthma, while 24 evaluated adherence to guideline recommendations on the assessment and management of acute asthma attacks. Differences in the care provided and asthma-related outcomes of patients managed by a specialist (respiratory physician or allergist), or a generalist (internist or general practitioner) were evaluated in 16 studies, of which 13 focused on long-term asthma management and three on acute attacks.

Risk of bias

Most studies evaluating strategies to improve implementation of guideline recommendations were at high/serious risk of bias (tables e4). Entirely appropriately, given that the implementation strategies

were targeted at improving guideline adherence by clinical teams, all the included interventional trials were cluster randomised and therefore potentially at risk of selection and detection bias. Moreover, several trials did not evaluate asthma-related outcomes and it was not always clear if this represented reporting bias. Moderate or serious risk of bias was also identified for most observational studies, due to confounding, participant selection, and often outcome selection as well. Only one longitudinal evaluation of the primary care practices in Bavaria was deemed to be at low risk of bias (Table e4).

High risk of methodological bias was identified in all 16 studies comparing care provision by Specialists and generalists apart from two observational studies that were deemed of low risk (table e4). The two RCTs were at high risk of selection and detection bias, while there were concerns regarding unaddressed confounding for most of the included observational studies (specifically confounding because Specialists tended to care for patients with more severe/ uncontrolled asthma, and more severe acute attacks than Generalists).

Strategies to improve adherence to guideline recommendations for long-term management of asthma. (Aim 2)

We identified 27 RCTs or cluster RCTs, 19 before-after studies, and six parallel comparative cohort studies, evaluating strategies for improving adherence to asthma guidelines (figure 2, tables 4, e5). All but three studies were conducted in primary care settings. Specific interventions included the provision of additional clinical input by a specialist HCP (usually a specialist nurse or pharmacist, 13 studies)[29,30,31,32,33,34,35,36,37,38,39,40], medical education (12)[41,42,43,44,45,46,47,48,49,50,51,52], computer decision-support systems (7)[53,54,55,56,57,58,59], introduction of asthma care pathways (4)[60,61,62,63], new local or national guideline (4)[64,65,66,67], or the participation of the centre in asthma-related clinical trials (1)[68]. Multifaceted quality improvement implementation strategies were evaluated in 11 studies[51,69,70,71,72,73,74,75,76,77,78,79].

Process outcomes were evaluated in most studies (46/52, 88.5%), of which 33 (71.7%) demonstrated improved adherence to guideline recommendations. The impact on asthma-related outcomes was evaluated in 31/52 (59.6%) studies. Only 18/31 (58.1%) showed any clinical benefit. Of note, this evaluation included the only observational study at low risk of bias, a large (n=109,042 patients) multifaceted quality improvement initiative conducted in Bavarian primary care[73].

Findings stratified by the type of intervention are summarized in figure 2 and table e5. The introduction of additional specialised HCPs support for patient care (such as a respiratory trained nurse or a pharmacist) into the primary setting was evaluated in 13 studies including large cluster RCTs

of high risk of bias and observational studies that were deemed at moderate risk of bias. Most studies demonstrated improvement in process outcomes and many also demonstrated clinical benefits.

Multifaceted quality improvement projects were assessed by 11 studies including three cluster RCTs, that were of high risk of bias, and several before-after studies, including four that were deemed low or moderate risk of methodological bias. Process and clinical benefits were demonstrated in most cases, including all the low and moderate risk of bias studies. However, it should be noted that two of the three cluster RCTs did not show process benefits and the only RCT evaluating clinical outcomes did not demonstrate any benefit either.

A number of studies evaluated specific strategies for improving guideline adherence such as computer decision-support systems, medical education, asthma care pathways with some promising results though typically in studies which combined several interventions. For example, introduction of an asthma care pathway or computer decision support system were more effective when paired with an educational component. The introduction of new guidelines with or without a training component appeared the least effective method for improving adherence. Use of interactive and case-based learning methods appeared more effective than simple lectures or printed training material.

Strategies to improve adherence to guidelines on the assessment and management of acute asthma attacks (Aim 2)

Three of the eligible studies were cluster RCTs, 17 were before-after and four were comparative cohort studies with concurrent and/or historical controls (Figure 3, Tables 1, E6). Three of the included studies were conducted in primary care, while the remainder were conducted in a hospital setting (mostly in emergency departments). Specific interventions included the introduction of acute asthma care pathways (n=12)[80,81,82,83,84,85,86,87,88,89,90,91], of additional patient specific input by a specialised health professional (1)[92], of a computer decision support system (1)[93], or of a national clinical guideline (1)[94], or the provision of medical education (1)[52]. Nine studies (including the two RCTs) evaluated multi-faceted quality improvement initiatives[95,96,97,98,99,100,101,102,103].

Process outcomes were evaluated in all but one study (23/24, 95.8%), and 18/23 (78.3%) showed a beneficial impact on adherence to treatment recommendations. Clinical outcomes were evaluated in 11 (45.8%) studies, and a clinical benefit was evident in only 3 of them (27.3%).

Acute asthma care pathways were evaluated in eight observational studies. All were deemed high risk of bias except for two that were moderate. Overall, asthma care pathways appeared effective in improving process but not clinical outcomes. Multifaceted quality improvement processes, evaluated

in two cluster RCTs and six observational studies, including two that were at moderate risk of bias, showed beneficial effect on process, and possibly on clinical outcomes. Data about the clinical effectiveness of other interventions were not reported.

Differences in process and clinical outcomes of patients managed by a specialist or a generalist (Aim 3)

Diagnosis, assessment and/or management of long-term asthma by Specialists (respiratory physicians or allergists) compared to Generalists (general physicians or general practitioners) was evaluated in two RCTs (both at high risk-of-bias) totalling 617 participants[104,105], and 14 observational studies, including six large studies using routine health databases (three cross-sectional and three longitudinal studies)[106,107,108,109,110,111], and smaller cross-sectional studies, including audits (figure 4, table e7)[112,113,114,115,116]. Management of acute asthma attacks was evaluated in three audits, totalling 1,838 participants[117,118,119].

Adherence to guideline recommendations was evaluated in 10/12 studies, showing significantly better adherence by Specialists, both for long-term asthma management and acute asthma attacks. Four of five studies showed that Specialists' care was associated with improved clinical outcomes including one cross-sectional study at low risk-of-bias which demonstrated differences in specialist/general practitioner diagnosis.

DISCUSSION

Summary and interpretation of results

Aim 1: Adherence to international asthma guidelines by HCPs of different specialties

The three online questionnaires gathered a good sample of approximately 1,500 international participations in total spanning primary, secondary and tertiary care. These diverse settings clearly influenced responses despite participants being advised that they had access to all diagnostic and management facilities. For example, diagnostically, Generalists favoured serial home peak flows to test for flow variability, whereas Respiratory and Allergy doctors would request FeNO which reflects familiarity and the context of their practice. Similarly, Allergy doctors were confident in identifying T2 and non-T2 phenotypes, a distinction which appeared to have little relevance for Respiratory doctors or Generalists, despite the increasing recognition of disease heterogeneity[120]. However, possible differences in the terminology used across the respondents' group may also be the cause of

the latter observation; characteristically, the terms used in severe asthma guidelines are eosinophilic and non-eosinophilic asthma[121,122].

Guidelines recognise both the importance of assessing characteristic symptom patterns and undertaking objective tests in order to make a diagnosis of asthma[17,18]. The poor sensitivity and specificity of many investigations[17,18] was reflected in the 'certainty' with which participants (in all groups) diagnosed the mild T2 patient as having asthma and offering treatment despite normal spirometry and no significant bronchodilator reversibility. Concerningly, in the severe cases, far from all participants would check the patient for comorbidities (ranging from 66% to 93.4%).

There was general agreement on core management strategies (role of intranasal corticosteroids, action plans, checking inhaler technique and adherence, supporting smoking cessation, treatment of nasal symptoms) but the clinical context of respondents influenced selection of other treatment modalities. For example, Allergy doctors prioritised immunotherapy or biologicals, while tiotropium and pulmonary rehabilitation was chosen more often by Respiratory doctors and Generalists. The importance of oral steroids in an acute attack was not in doubt, but the dosages chosen varied considerably (from 1mg/kg to 1mg/kg/day and 50mg prednisolone). GINA guidelines currently recommend for adults 1mg/kg/day and up to 50mg/day of prednisolone or equivalent for 5-7 days[17].

GINA highlights the need to adapt asthma management strategies to enable implementation within local/national healthcare settings[17]. Whilst some of the discrepancies identified in our survey may be due to poor dissemination or lack of knowledge, a considerable proportion of the diverse responses from Allergy/Respiratory doctors and Generalists are likely to reflect adaptations consistent with their different clinical settings. Effective implementation strategies are considered in the evidence from the systematic reviews.

Aim 2: Effectiveness of strategies to improve implementation of guideline-recommended interventions

Our systematic reviews evaluated various strategies for improving implementation of asthma guidelines. The strategies were grouped into broad categories, however inconsistencies were observed in the results of studies evaluating strategies in each category, complicating interpretation. The main sources of heterogeneity were differences in the characteristics of individual interventions, in the methods for delivering the intervention (e.g. engagement and training of the clinical staff), the context in which the interventions were delivered and the outcomes assessed.

Patient-specific input by additional specialized health professionals was evaluated in 13 studies, including large cluster RCTs of high risk of bias and observational studies that were deemed at

moderate risk of bias. The vast majority of studies evaluating this intervention demonstrated improved process outcomes and most also demonstrated clinical benefits. However, cost-effectiveness of this approach has not been evaluated, and it is not clear if this benefit is sustained after the trial is completed in case the additional support is withdrawn. In contrast, a large-scale cluster RCT in which existing primary care staff were upskilled was not effective[37].

Multicomponent quality improvement initiatives incorporating a range of implementation strategies addressing multiple challenges to guideline adherence (such as training health professionals, on-going audit and feedback/benchmarking, introduction of asthma care pathways, identification and resolution of organisational barriers[123]) appeared the most effective. Characteristically, the strategies employed in the three studies that did not show improved outcomes (either clinical or process) only included two components; audit and feedback to clinicians. Similarly, findings from studies evaluating a single intervention were in general less consistent. Multifaceted quality improvement projects incorporating a range of implementation strategies addressing challenges to guideline adherence at the level of the patient, health professional and health system were more likely to be effective. This reflects recognition of the need to take a whole systems' approach to improving practice[124,125].

Asthma care pathways were mostly evaluated in high-risk of bias studies, which however showed clinical and process benefits. Studies evaluating other interventions were mostly at high risk of bias and their findings were either inconsistent (computer decision-support systems, medical education), or negative (introduction of a guideline, participation in clinical trials).

Some studies with longer observation periods[97,103] noted that the impact of the interventions tended to wane and needed continuous reinforcement, for example through audit, feedback and re-training.

Strategies for improving adherence to guidelines have been evaluated in previous systematic reviews, with consistent findings. Two systematic reviews assessing a broad range of strategies concluded that multifaceted quality improvement programmes were more effective than single component interventions, especially those based explicitly on a theoretical framework, with a strong educational component including a combination of instructional modalities, longer duration[126], and those promoting engagement at the level of the patient, health professionals and organisation[127]. Other systematic reviews focusing on specific approaches concluded that input by pharmacists[128] and asthma care protocols[129] could be beneficial, while medical education[130] and computer decision support systems[131] were not effective, though it was not clear whether limitations of the interventions or implementation methods were responsible for this lack of observed benefit.

Aim 3: Comparison of process and clinical outcomes in patients managed by Specialists or Generalists

This systematic review was informed by fewer studies, most of which were observational and at high risk of bias. Almost all studies showed that specialist care was associated with better adherence to guideline recommendations, with some suggestion in six of the seven studies evaluating clinical outcomes these may also be improved. It should be noted that specific findings from some of the older studies' may no longer be applicable. For example, two of these studies date from the early days of ICS prescribing when Generalists may have been more cautious[105,110]. Improved diagnosis by Specialists in a cross-sectional study at low risk of bias, might reflect better access to investigations[119]. However, Specialists care was consistently associated with better outcomes in more recent studies. It should also be highlighted that only one extensive observational study evaluating process outcomes and a smaller observational study evaluating clinical outcomes were low risk of bias, with the remaining being deemed high risk.

Asthma diagnosis, assessment and management are complex and the respective guidelines are updated frequently, making it more challenging for the generalist to keep updated. Robust, continuous, multifaceted quality improvement projects will be required to ensure that patients receive high-quality care with locally agreed referral pathways for specialists' advice.

Strengths and limitations

The survey results provided an insight into asthma management at international level with a good number of responses from across all levels of care. A limitation to our results is that the second survey participants were not asked whether they had also taken part in the first survey, hence we cannot be sure of the total number of unique participants. Furthermore, the setup of the surveys did not facilitate analysis of the results according to the country in which the participants practised and, we are unable to establish whether variations in the answers received may have been country-related. Finally, a higher proportion of the participants were respiratory physicians. However, all surveys included adequate responses from allergists and generalists, that allowed the panel to derive informed conclusions.

Our systematic reviews have a number of limitations. The study protocol was not made publicly available, however, it was developed prospectively and submitted to the ERS and EAACI. Most of the included studies were at high risk of bias, which reduces the confidence in the findings. Most included trials were cluster RCTs. Although this is the optimal study design for evaluating implementation targeted at clinical teams, they are at high risk of selection, performance and detection bias based on

the Cochrane risk of bias tool. Confounding was the main source of bias in observational studies and despite several studies accounting for confounding factors, adjustments were not deemed adequate in most cases. In the systematic review comparing the outcomes of patients evaluated by Specialists versus Generalists, a key confounder was that Specialists tend to care for people with more severe or uncontrolled asthma. Better outcomes among these patients could either reflect better quality of care provided by Specialists, or that there was greater capacity for improvement. We were not able to conduct meta-analyses, due to the considerable clinical and methodological heterogeneity, but our results are presented in detail, both tabulated and illustrated in harvest plots to facilitate interpretation.

Last, but not least there is significant heterogeneity among the current international asthma guidelines, thus this might be reflected in the interventions meant to improve adherence.

Implications for practice and research

Asthma is a heterogeneous disease, meaning that its diagnosis, assessment and management are complex[17,18]. In parallel, it is the focus of intensive research that leads to continuous change to clinical practice guidelines and practice, increasingly incorporating precision medicine interventions[22],[132]. As a result, implementation of asthma guidelines and delivery of high-quality, evidence-based medicine is challenging and often suboptimal[133,134,135]. Our findings suggest that continuous multifaceted quality improvement processes can enhance adherence to guidelines. Additional input by a Specialist, either a Respiratory Physician, Allergist, or a respiratory trained nurse or pharmacist, also appears to improve guidelines adherence and clinical outcomes, although further data is needed to confirm sustainability of these findings. Moreover, the feasibility and cost-effectiveness of these approaches should be evaluated.

Our survey revealed significant variability in practice, across different clinical settings, that reflects guideline adaptations in a real-life context, where different diagnostic or therapeutic options and sources are available. Guideline panels need to consider these practical differences when developing clinical recommendations, and to offer options for evidence-based practice in different clinical settings.

Systematic literature review also indicated a potential association of specialist care with improved process and clinical outcomes. However, more data are needed, as confidence was limited on this finding. Undoubtedly, the complexity of asthma care imposes the need for a multidisciplinary approach to the diagnosis and management of these patients. As a result, it is now widely

recommended that patients with severe asthma should be managed in specialised severe asthma clinics[11,17,18,121,122]. However, the diagnosis and management of patients without severe asthma is also complex, but it is still unclear when generalist or specialist care is necessary[11,17,18,121,122]. This complicates the work of both generalists and specialists, and -as suggested by our SR- may also impact on the clinical outcomes of individuals with asthma. Therefore, data are needed to inform standardization in the indications for referral of patients for specialist review, that should be tailored to the balance of resources required for continuous multifaceted quality improvement processes in primary care versus the evaluation of an increased proportion of individuals with asthma in specialty clinics. In the meantime, locally agreed referral pathways to specialists are crucial both for Generalists and for Specialists from different disciplines who have different approaches to diagnostic uncertainty and managing patients with poorly controlled asthma.

The emergence of the Coronavirus Disease 2019 (COVID-19) has extensively affected the care of people with asthma, mainly by replacing physical appointments with virtual encounters, while in parallel reinforcing telemonitoring technologies[136,137]. It is recognized that to some extent these practice changes introduced during 2020 will outlive the pandemic, as they appear effective, convenient for patients and require fewer resources[138,139,140,141,142,143]. An opportunity emerges to use these new technologies to enhance adherence to guidelines. For example, efficient methods for capturing disease characteristics in a computer-usable format could facilitate patient profiling and strengthen decision support systems. Such interventions are already being evaluated in other disease areas with promising preliminary results[144,145].

Box 4: Key messages

- Implementation of guidelines is different across different asthma management settings.
- Guideline recommendations need to account for differences in resource availability across the various asthma care settings, including primary care.
- Continuous multifaceted quality improvement processes can improve guidelines adherence.
- Additional input from specialised health professionals could also be effective towards improving guidelines adherence. However, this is unlikely to be sustainable unless long-term funding is available.
- Locally agreed referral pathways to specialists are crucial both for Generalists and Specialists from different disciplines who have different approaches to diagnostic uncertainty and managing patients with poorly controlled asthma.
- More data are needed to evaluate differences in process and clinical outcomes among patients managed by Generalists or Specialists and to facilitate standardization in the indications for referral of patients for specialist review.

CONCLUSION

This evaluation conducted as a joint initiative between EAACI and ERS showed a significant gap in implementing asthma guidelines in real life. This calls for action on several fronts: a) guideline developers should consider the heterogeneity of settings for asthma management in real life and tailor their recommendations accordingly; b) multifaceted interventions should receive better funding to improve adherence to guidelines; c) validated referral pathways for uncontrolled asthma or for uncertain diagnosis should be prioritized.

Tables and figures:

Table 1. Systematic review questions. **A.** SR-1: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and long-term management of asthma. **B.** SR-2: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and management of acute attacks. **C.** SR-3: Process and clinical outcomes in patients managed by Specialists or Generalists.

Table 2. Health care profession and subsequent categorisation in the analyses of the survey.

Table 3. Preferred diagnostic procedure in different subtypes of asthma, as reported in the online survey. *P-values pertain to comparisons among the three groups, using chi-squared test.

Table 4. Types of studies evaluating the adherence to asthma guidelines and the proportion of studies demonstrating beneficial (a) clinical and (b) adherence outcomes, among the studies evaluating such outcomes.

Figure 1. PRISMA flow diagram.

Figure 2. Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for asthma assessment and maintenance management.

Figure 3. Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for acute asthma attacks assessment and management.

Figure 4. Harvest plot summarizing the findings of studies evaluating differences in the adherence to asthma guidelines by Specialists or Generalists.

Table 1. Systematic review questions.

A. SR-1: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and long-term management of asthma.

Population	Patients with a clinical diagnosis of asthma. Patients with a clinical suspicion of asthma, for studies evaluating asthma diagnosis.
Intervention	Interventions aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and long-term management of asthma.
Comparator	Any other intervention aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and long-term management of asthma, or no intervention
Outcomes	Clinical outcomes such as frequency of acute attacks, episodes of hospitalisation, asthma symptoms, or quality of life. Process outcomes, such as adherence to specific guidelines components (e.g. prescription of inhaled corticosteroids for patients requiring maintenance treatment, or delivery of smoking cessation advice).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.

B. SR-2: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and management of acute attacks.

Population	Patients with a clinical diagnosis of an acute asthma attach. Patients with a clinical suspicion of acute asthma attach, for studies evaluating asthma attack diagnosis.
Intervention	Interventions aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and management of acute asthma.
Comparator	Any other intervention aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and management of acute asthma, or no intervention
Outcomes	Clinical outcomes such as need for hospital admission, duration of symptoms, treatment success or failure, need for intubation or mechanical ventilation. Process outcomes, such as adherence to specific

	guidelines components (e.g. prescription of oral corticosteroids for all patients with an acute attack leading to an emergency presentation or hospital admission).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.

C. SR-3: Process and clinical outcomes in patients managed by Specialists or Generalists.

Population	Patients with a clinical diagnosis of asthma or acute asthma attack. Patients with a clinical suspicion of asthma or acute asthma attack, for studies evaluating asthma or acute asthma attack diagnosis, respectively.
Exposure A	Management by an asthma specialist (respiratory physician or allergist).
Exposure B	Management by a generalist (general practitioner or internist, not specialised in asthma).
Outcomes	For studies evaluating the diagnosis, assessment or long-term management of asthma: Clinical outcomes such as frequency of acute attacks, episodes of hospitalisation, asthma symptoms, or quality of life. Process outcomes, such as adherence to specific guidelines components (e.g. prescription of inhaled corticosteroids for patients requiring maintenance treatment, or delivery of smoking cessation advice). For studies evaluating the diagnosis, assessment or management of acute asthma attacks: Clinical outcomes such as need for hospital admission, duration of symptoms, treatment success or failure, need for intubation or mechanical ventilation. Process outcomes, such as adherence to specific guidelines components (e.g. prescription of oral corticosteroids for all patients with an acute attack leading to an emergency presentation or hospital admission).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.

Table 2. Health care profession/level of training and subsequent categorisation in the analyses of the survey

Category	n (%)	Categories in the analyses
1st Survey: Mild T2 & Severe T2 asthma		
Allergy – Asthma specialist	22 (2.5)	Allergy doctor
Allergy specialist	133 (15.2)	Allergy doctor
Trainee in Allergy	9 (1.0)	Allergy doctor
Respiratory – Asthma specialist	123 (14.1)	Respiratory doctor
Respiratory doctors	456 (52.1)	Respiratory doctor
Trainee in Respiratory Medicine	34 (3.9)	Respiratory doctor
General Practitioner	48 (5.5)	Generalist
Internist	28 (3.2)	Generalist
Specialist nurse	13 (1.5)	Generalist
Trainee General Practitioner	4 (0.5)	Generalist
Trainee in Internal Medicine	4 (0.5)	Generalist
Nurse trainee	1 (0.1)	Generalist
2nd Survey: non T2 asthma		
Allergy – Asthma specialist	30 (4.4)	Allergy doctor
Allergy specialist	163 (24.0)	Allergy doctor
Trainee in Allergy	12 (1.8)	Allergy doctor
Respiratory – Asthma specialist	80 (11.8)	Respiratory doctor
Respiratory doctors	245 (36.1)	Respiratory doctor
Trainee in Respiratory Medicine	13 (1.9)	Respiratory doctor
General Practitioner	99 (14.6)	Generalist
Internist	16 (2.4)	Generalist
Specialist nurse	14 (2.1)	Generalist
Trainee General Practitioner	4 (0.6)	Generalist
Trainee in Internal Medicine	2 (0.3)	Generalist
Nurse trainee	1 (0.2)	Generalist

Table 3. Preferred diagnostic procedure in different subtypes of asthma as reported in the online survey. *P-values pertain to comparisons among the three groups, using chi-squared test.

	Allergy doctors (%)	**Respiratory doctors (%)**	**Generalists (%)**	P-value*
Mild T2 asthma				
Spirometry with reversibility test	95.0	96.4	86.9	0.001
Peak flow	24.1	27.8	39.3	0.04
FeNO	49.0	58.7	41.7	<0.0001
Blood Eosinophils	57.2	73.7	63.1	<0.0001
Total IgE	49.7	63.6	41.7	0.006
Skin prick test	93.1	65.4	50.0	<0.0001
Specific IgE	53.1	38.0	32.1	0.001
Chest X-ray	36.6	55.7	23.8	<0.0001
ENT examination	31.7	31.4	29.8	0.95
Bronchoscopy	0	2.5	1.2	0.12
Bronchial provocation	19.3	31.9	20.2	0.002
Bacterial culture	4.1	7.4	7.1	0.38
Detailed history	70.3	68.1	66.7	0.82
Chest auscultation	55.9	48.3	41.7	0.10
Serial peak flow	53.1	62.9	75.0	0.004
Severe T2 asthma				
Spirometry with reversibility test	98.0	96.4	85.1	0.001
Peak flow	19.2	24.1	25.5	0.55
FeNO	74.8	79.9	48.9	0.004
Blood Eosinophils	79.8	85.9	68.1	0.006
Total IgE	60.6	77.6	36.2	<0.0001
Skin prick test	99.0	78.4	57.4	<0.0001
Specific IgE	55.6	41.0	34.0	0.01
Chest X-ray	39.4	59.8	27.7	<0.0001
ENT examination	40.4	34.6	27.7	0.30
Bronchoscopy	1.0	1.7	2.1	0.86
Bronchial provocation	8.0	10.8	4.3	0.30
Bacterial culture	9.1	8.6	8.5	0.99
Detailed history	78.8	79.5	80.8	0.96
Chest auscultation	83.8	81.7	76.6	0.57
Serial peak flow	37.4	41.3	48.9	0.42
Check prescriptions	76.8	85.3	83.0	0.13
Assess inhalation technique	92.9	91.7	85.1	0.26

Non-T2 asthma				
Spirometry with reversibility test	65.4	69.5	49.2	<0.0001
Peak flow	14.6	21.0	28.4	0.009
FeNO	50.2	49.7	26.9	<0.0001
Blood Eosinophils	53.2	61.2	38.1	<0.0001
Total IgE	44.9	479	19.4	<0.0001
Skin prick test	26.3	14.2	9.0	<0.0001
Specific IgE	22.4	25.2	11.9	0.007
Chest X-ray	49.30	55.9	30.6	<0.0001
ENT examination	30.2	23.1	11.2	<0.0001
Bronchoscopy	1.5	3.2	2.2	0.42
Bronchial provocation	1.5	4.1	2.2	0.17
Bacterial culture	17..1	17.8	4.5	0.001
Detailed history	65.8	67.8	53.7	0.01
Chest auscultation	68.8	71.2	61.2	0.12
Occupational evaluation	55.1	66.3	56.0	0.02
Check adherence	66.3	71.0	59.7	0.06
Assess inhaler technique	72.2	79.9	64.9	0.002

Table 4. Types of studies evaluating the adherence to asthma guidelines and the proportion of studies demonstrating beneficial (a) clinical and (b) adherence outcomes, among the studies evaluating such outcomes.

	N	RCTs	Before-after	Comparative observational study	Beneficial clinical outcomes	Beneficial process outcomes
Assessment and management of asthma during stable disease state						
Additional patient specific input by a specialised health professional	13	8	2	3	8/12 (66.7%)	10/11 (90.9%)
Asthma care pathway	4	1	3		2/2 (100%)	3/3 (100%)
Computer decision-support systems	7	6	1		3/5 (60%)	4/7 (57.1%)
Introduction of a local or national guideline	4	2	1	1	0/1 (0%)	2/4 (50%)
Medical education	12	7	5		1/4 (25%)	5/10 (50%)
Quality improvement process	11	3	7	1	4/6 (66.7%)	8/10 (80%)
Participation in a clinical trial	1			1	0/1 (0%)	0/1 (0%)
Assessment and management of acute asthma attacks						
Acute asthma care pathway	12		11	1	1/8 (12.5%)	10/12 (83.3%)
Additional patient specific input by a specialised health professional	1			1	0/0 (N/A)	1/1 (100%)
Computer decision-support systems	1		1		0/0 (N/A)	1/1 (100%)
Introduction of a local or national guideline	1		1		0/0 (N/A)	0/1 (0%)
Medical education	1	1			0/0 (N/A)	0/1 (0%)
Quality improvement process	9	2	5	2	2/3 (66.7%)	6/7 (85.7%)

Figure 1. PRISMA Flow diagram

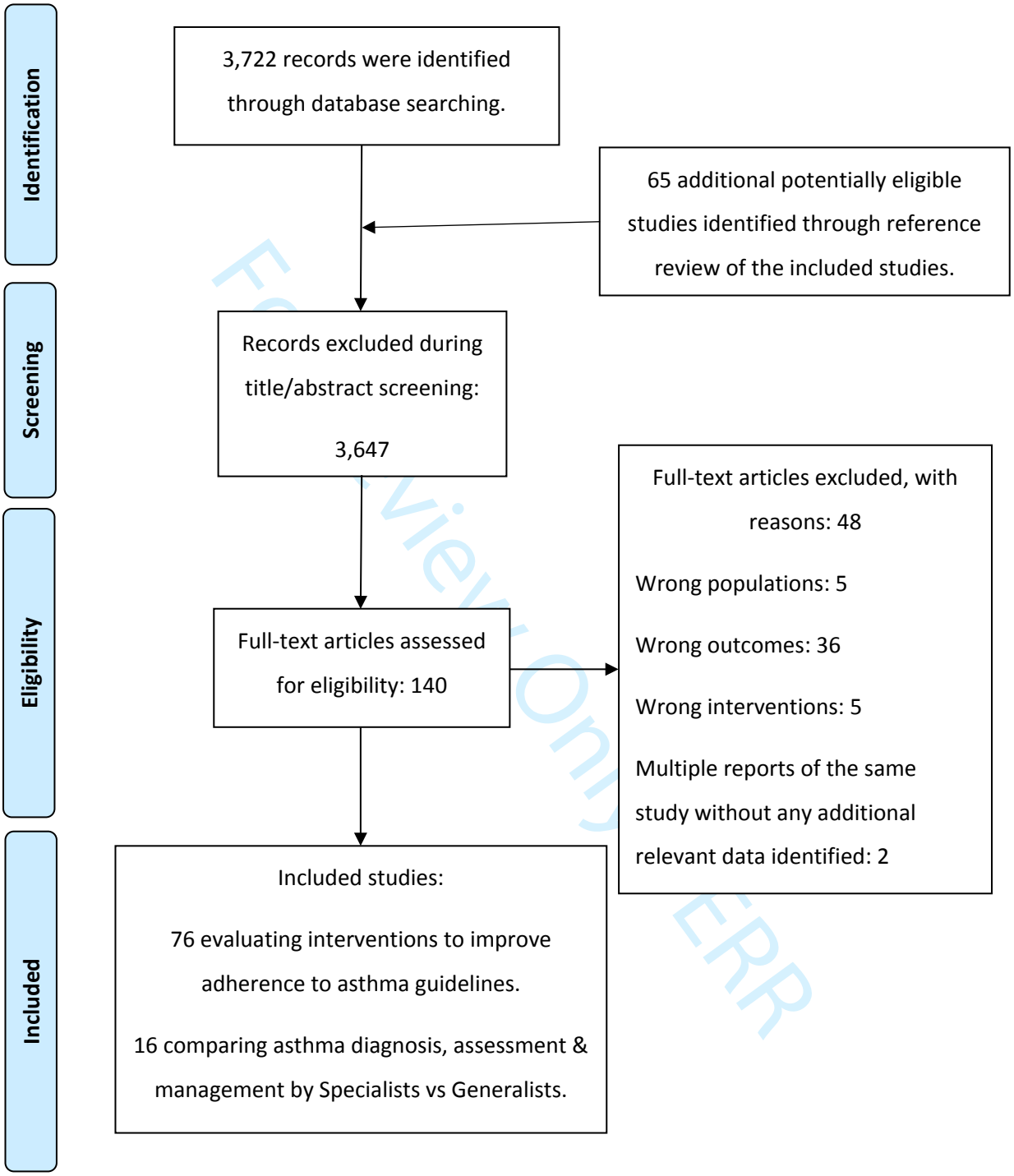


Figure 2. Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for asthma assessment and maintenance management.

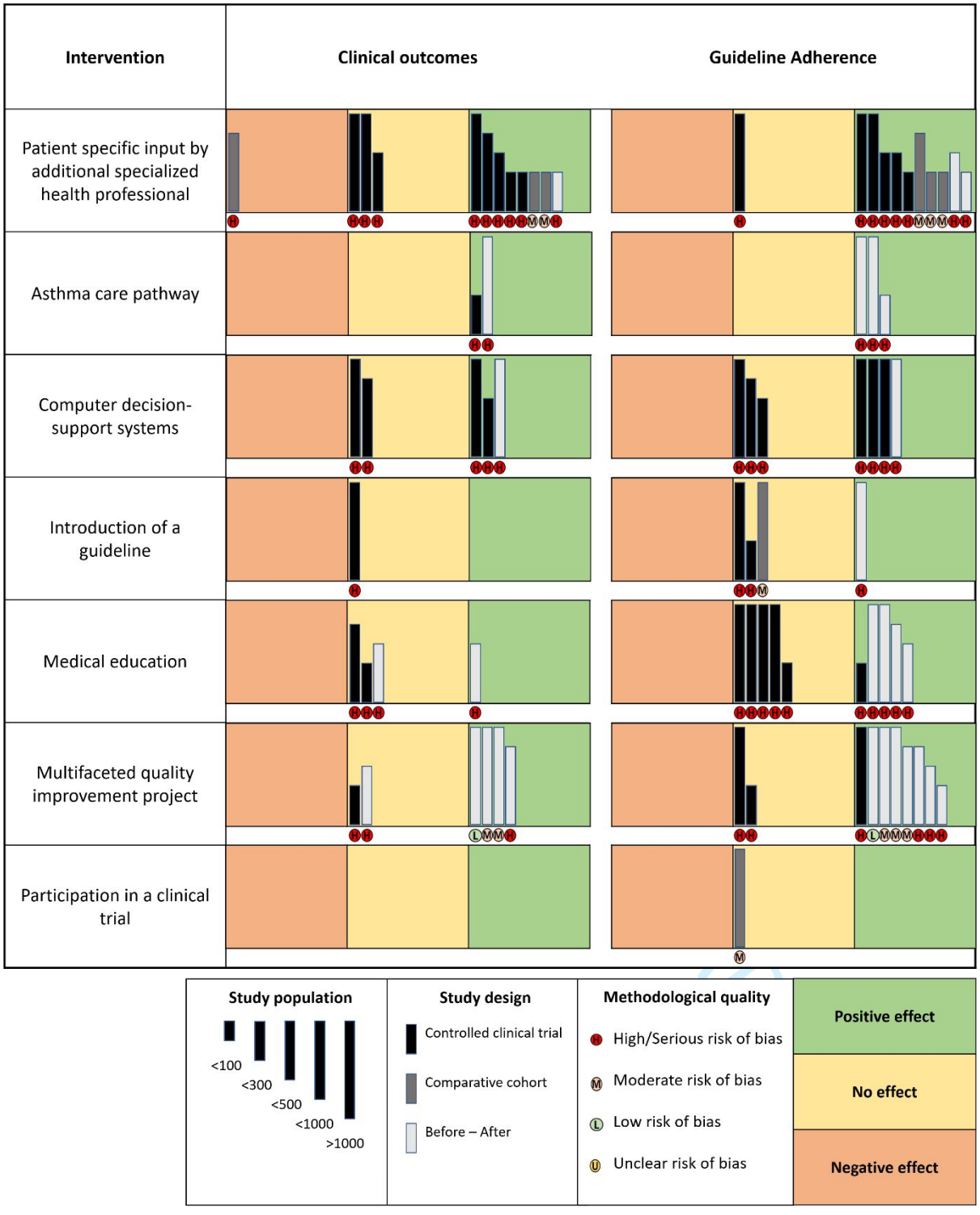


Figure 3. Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for acute asthma attacks assessment and management.

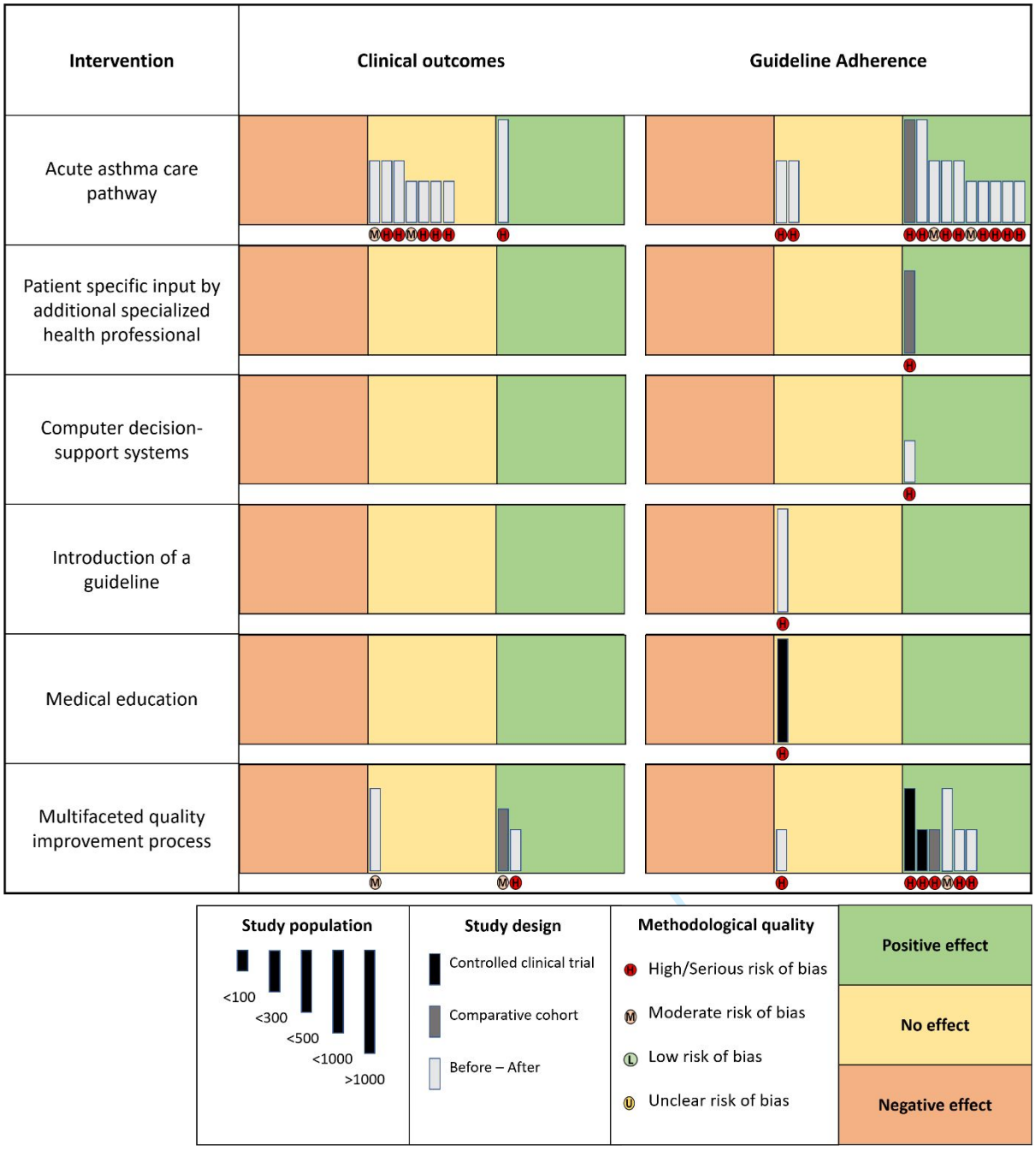
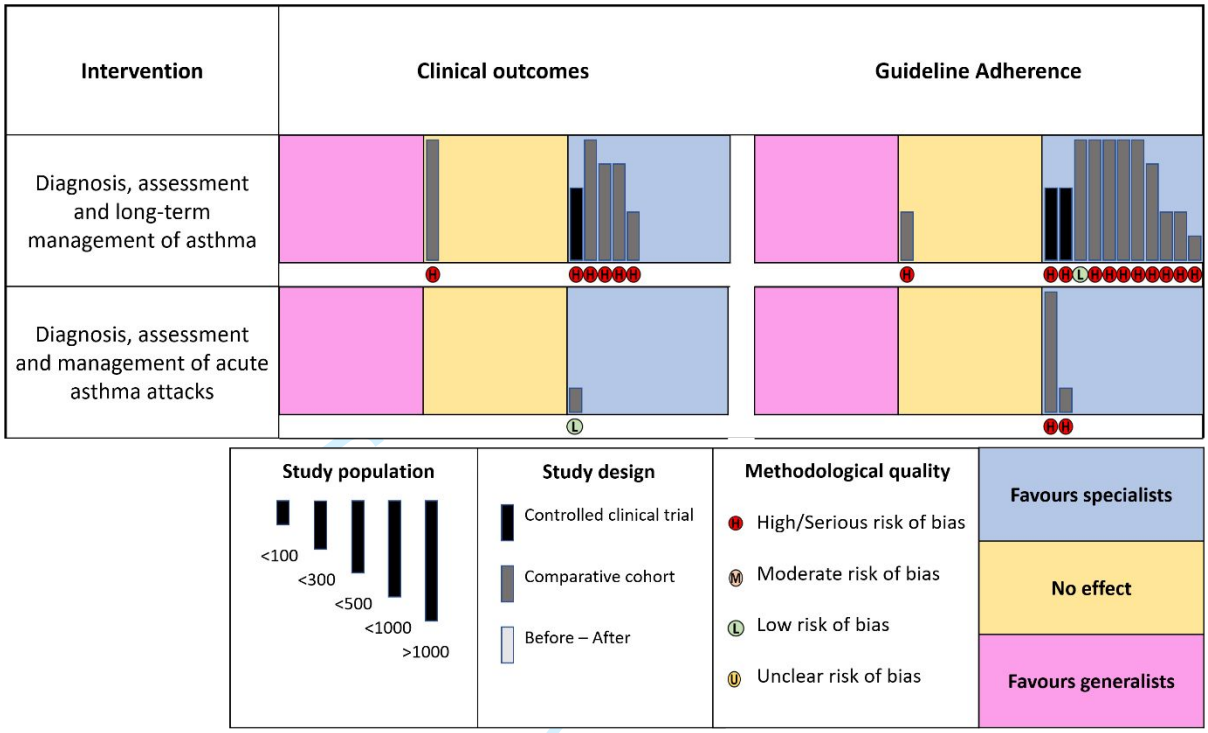


Figure 4. Harvest plot summarizing the findings of studies evaluating differences in the adherence to asthma guidelines by Specialists or Generalists.



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ERS/EAACI statement on adherence to international adult asthma guidelines

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Abstract: (2050 words)

~~Clinical practice g~~Guidelines ~~based on the best available evidence,~~ aim to standardize and optimize asthma diagnosis and management. Nevertheless, adherence to guidelines is suboptimal and may vary across ~~there are concerns that particularly between~~ different ~~groups of~~ healthcare professional~~s~~ (HCP~~s~~) groups~~, adherence to guidelines is suboptimal~~.

Further to these concerns, thi~~se aims of this~~ ERS/EAACI Statement aims~~were~~ (1) via an international online survey, to evaluate ~~and compare~~ the understanding of and adherence to international asthma guidelines by HCPs of different specialties, (2) via systematic reviews ~~of the literature~~, to assess ~~effectiveness of~~ strategies focused at improving implementation of guideline-recommended interventions, and compare process and clinical outcomes in patients managed by ~~Specialists (respiratory physicians or allergists) or Generalists (internists or general practitioners)~~HCP of different specialties.

The online survey identified discrepancies between HCPs of different specialties which may be due to poor dissemination or lack of knowledge of the guidelines but also a reflection of the adaptations made in different clinical settings, based on available resources~~HCPs working in different clinical settings make, based on their resources~~. The systematic reviews demonstrated that multifaceted quality improvement initiatives addressing multiple challenges to guidelines adherence~~, or the input from additional specialized HCPs~~ are most effective in improving guidelines adherence. ~~More data are needed to evaluate d~~Differences in ~~process and clinical~~ outcomes between~~among~~ patients managed by Generalists or Specialists should be further evaluated.

~~Our results reveal a need for G~~guidelines need to consider the heterogeneity of real-life settings for asthma management and tailor their recommendations accordingly. Continuous, multifaceted quality improvement processes are required to optimize and maintain guidelines adherence. Validated referral pathways for uncontrolled asthma or ~~for~~ uncertain diagnosis are needed.

Take home message: @EuroRespSoc @AllergyEAACI Statement: Guidelines need to account for differences in resource availability across various asthma care settings. Continuous, multifaceted quality improvement processes are needed to optimize and maintain guidelines adherence.

INTRODUCTION

In the European Union, over 20 million people suffer from asthma[1]. During the 1990s there was a rapid decrease in asthma mortality[2], probably related to the increased use of inhaled corticosteroids (ICS)[3]. However, during the last decade, asthma mortality rates have plateaued, and a consistently high proportion of patients have uncontrolled asthma[4,5]. As a result, many patients with asthma still have impaired quality of life and suffer from chronic respiratory symptoms, often including night-time symptoms, causing sleep disturbance, excessive daytime sleepiness and decreased work productivity[6,7].

The reason for this lack of improvement in achieving asthma control is multifactorial. Asthma is a chronic inflammatory airway disease needing regular long-term anti-inflammatory treatment for symptom control and prevention of acute attacks and/or lung function decline. ICS are the mainstay of asthma medication, but many patients do not adhere to regular treatment[8] with overreliance on short acting beta-agonists (SABAs), leading to under-treatment of the chronic inflammation[9]. Another possible explanation is the heterogeneity of asthma, so that subgroups of patients require different interventions, according to a personalized approach based on asthma phenotypes[10]. A proportion have severe asthma[11] and need to be identified and offered specific regimes such as biological treatment with anti-IgE, anti-IL5 or anti-IL4/IL13[12,13]. Other factors such as poor inhaler adherence and technique, lack of self-management support, exposure to triggers, unavoidable environmental factors, limited accessibility to diagnostic facilities and medication, could also contribute[14,15,16].

Clinical practice guidelines, based on available evidence, define disease control and risk of acute attacks and make recommendations to standardise and optimise asthma diagnosis and management. National and international asthma guidelines have been available since the 1990s and are continuously being updated[11,17,18]. However, there are concerns that adherence to guidelines is far from optimal and varies between different groups of healthcare professionals (HCPs)[19,20]. In addition, the 'one-size-fits-all' approach of guidelines (typically based on efficacy in highly selected populations evaluated in randomised controlled trials) limits perceived applicability and relevance in real-life practice[21]. Further to these concerns, we aimed (1) to evaluate and compare the understanding of and adherence to international asthma guidelines by HCPs of different specialties, (2) to assess effectiveness of strategies aimed at improving implementation of guideline-recommended interventions, and (3) to compare process and clinical outcomes in patients managed by Specialists (respiratory physicians or allergists) or Generalists (internists or general practitioners).

METHODS

This task force was formed by the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in 2015 and was chaired by two representatives from the ERS (AGM and CJ) and two from EAACI (OT and IA) who were responsible for project management and co-ordination. The task force was composed of experts from three ERS Assemblies (1- Respiratory clinical care and physiology, 5- Airway Diseases: asthma, COPD and chronic cough, and 6- Epidemiology and Environment), from four EAACI bodies (Asthma Section, Primary Care Interest Group, Executive Committee and Junior Members Assembly) and from the International Primary Care Respiratory Group (IPCRG) (JCS). It involved experts in respiratory medicine and science, allergy and general practice, and also a lay person with lived experience of asthma (BF). The co-chairs met in January 2017 and September 2018 and a face-to-face meetings of the task force was held in January 2019, with teleconferences and e-mail correspondence as required. All task force members signed conflict-of-interest statements at the beginning of the project and updated them at project finalisation or when any new relevant conflict appeared, in line with the ERS and EAACI procedures. This report was informed by an international online survey (Aim 1) and two systematic reviews (Aims 2 and 3).

On-line survey (Aim 1)

Three online questionnaires pertaining to different clinical cases were prepared by the panel and uploaded to the SurveyMonkey platform (available in the online supplement). The cases were not related to a specific clinical setting so that the questionnaires were applicable to all specialties targeted by the survey. The first scenario was a mild type 2 (T2) asthma, the second a severe T2 asthma, and the third a severe non-T2 asthma. T2 asthma is defined by the presence of eosinophilic inflammation driven via three pathways: IgE, IL-5 or IL-4/IL-13[22]. Allergic asthma is a sub-endotype of T2 asthma, frequently with childhood onset and associated with other atopic diseases (allergic rhinitis, atopic dermatitis, food allergy). Another sub-endotype is non-allergic eosinophilic asthma, with adult-onset, usually more difficult to control[22]. Non-T2 asthma is usually defined by the lack of eosinophilic inflammation[22]. Its mechanisms are less well described as opposed to T2 asthma[22].

Introductory questions collected participants' age, gender, specialty, level of training (trained or in training), and clinical setting. The T2 asthma questionnaires were sent out in May 2018 as a pair (mild T2 questions were completed prior to the severe T2 questions), and the non-T2 questionnaire was distributed in August 2018. Surveys were open for approximately 6 weeks. For most of the questions more than one answer could be chosen. Participants of the second survey were not asked if they had

also taken part in the first survey. After completion, a participant could not take the survey again on the same computer.

Both survey links were disseminated via mass emails with links to the online surveys, to relevant members of the participating organisations (EAACI: Asthma Section, ENT Section, Immunotherapy, Occupational Allergy, Allied Health and Primary Care Interest Groups, EAACI National Societies platform; ERS aforementioned assemblies; IPCRG). EAACI and ERS social media platforms supplemented the dissemination of the survey links.

Survey results were analysed based on the participants' specialty. Specialties were grouped into three main categories: i) 'Allergy Doctor' if participant indicated they were Allergy-Asthma Specialist, Allergy Specialist or Allergy Trainee, ii) 'Respiratory Doctor' if participant indicated they were an Asthma Specialist, Respiratory Doctor or Respiratory Medicine Trainee, iii) 'Generalist' if participant indicated they were General Practitioner, General Practitioner Trainee, Internist, Internal Medicine Trainee, Specialist Nurse or Nurse Trainee.

The results of the questionnaire answers are presented as % affirmative answers. Comparisons between the three groups were made using Chi-squared test. Stata 15 (Stata Corp, College Station, Texas USA) was used for the calculations.

Ethics approval was not necessary for this survey, as no personally identifiable data were collected.

Systematic review methods (Aims 2 and 3)

Two systematic reviews (SRs) were conducted to evaluate (Aim 2) the effectiveness of strategies to improve adherence to guidelines on the diagnosis, assessment and long-term/acute treatment of asthma, including maintenance and acute attacks management, and (Aim 3) the process and clinical outcomes in patients managed by Specialists (respiratory physicians or allergists) compared to Generalists (internists or general practitioners) (Table 1). The SRs followed Cochrane methodology[23]. Medline/PubMed was searched for studies published after 1990 (publication of the first asthma guideline[24]), using a search strategy that included controlled vocabulary and free search terms (available in the online supplement), to identify relevant studies. Reference lists of included studies and of any previous, relevant SRs were screened. Studies of any design addressing the two review questions were eligible if they assessed process outcomes (e.g. adherence to guideline recommendations) and/or asthma-related clinical outcomes. Two reviewers independently evaluated all identified abstracts for eligibility. The full texts of all potentially eligible manuscripts were similarly evaluated for inclusion by two reviewers. Disagreements were resolved by discussion between

reviewers. We extracted relevant data on study characteristics, process and clinical outcomes in a structured excel sheet. We evaluated methodological quality using the Cochrane Risk of Bias tool for randomised controlled trials (RCTs)[25] and the Risk Of Bias In Non-randomised Studies of interventions (ROBINS-I) for non-randomised studies[26].

As anticipated, we were not able to conduct meta-analyses, due to the significant methodological and clinical diversity, statistical heterogeneity, inconsistency, and incompleteness of outcomes reported in the included studies. Instead, we used narrative synthesis and present pertinent results of the included studies in a tabulated format. Findings are presented visually as harvest plots, which summarise the direction and significance of the effect on process and clinical outcomes for each of the studies along with information about study design, study population and methodological quality.[27,28]. To interpret the overall findings, we prioritised differences in clinical outcomes over process outcomes.

RESULTS

Survey results (Aim 1)

Survey 1: Mild T2 asthma and Severe T2 asthma

Of the 784 participants who started the mild T2 questionnaire, 507 also started the severe T2 asthma questions. The majority (70.8%) of the participants (n=784) were Respiratory Doctors as opposed to 18.5% and 10.7% who were Allergy Doctors and Generalists, respectively. The participants' speciality and categorisation for the sub-group analysis are summarised in Table 2. Most (45.2%) were tertiary care Specialists, 32.6% and 22.2% worked in secondary or primary care respectively.

Mild T2 asthma

Box 1.

Case vignette 1.

A 22-year-old female, non-smoker, maths student attends for a consultation in October complaining about occasional chest tightness and cough (especially when playing tennis), during late spring to mid-summer the last 4 years. She has never used any inhalers for her chest symptoms. Regular chest auscultation provides you with normal lung sounds.

She also mentions that during the same months she has been experiencing watery eyes and nose, nasal congestion as well as sneezing. These symptoms began early at adolescence and have been managed with as needed, over the counter antihistamines. She was diagnosed with eczema and egg allergy as a toddler with both conditions having resolved by the age of 10 years, which was the age she was last evaluated in an allergy clinic. She has a cat at home.

Additional information

Chest auscultation with fierce exhalation provides normal sounds. You had the possibility of performing spirometry and received the following outcomes: baseline spirometry resulted in FEV1/FVC ratio 0.75 and administration of 400 mcg salbutamol increased FEV1 by 10% (150 ml). What is your diagnosis and how would you manage the patient?

Follow-up

The patient comes back during the pollen season. She reports episodes of chest tightness and cough especially early in the morning when she is walking to work through a park and if walking back home late evening. She additionally mentions wakening up at night due to chest tightness and nasal blockage. She has been avoiding playing tennis because of these symptoms. She is receiving her antihistamine daily but no nasal spray. Regular chest auscultation provides you with normal lung sounds. Spirometry with reversibility results in 13% (220 ml) increase in FEV1 post the bronchodilator administration.

Responses about preferred diagnostic procedures are presented in Table 3. Spirometry with reversibility was the preferred diagnostic test in all groups. Home serial peak flow measurements were significantly more popular amongst the Generalists than the other groups and a third of the Respiratory Doctors would undertake bronchial provocation at the initial consultation compared to a

fifth of the other two groups. Of note, auscultation of the chest during forced expiration was seen as helpful by less than half of the Respiratory Doctors and Generalists. Statistically significant differences between the three groups were noted for the measurement of the fractional exhaled nitric oxide (FeNO), blood eosinophils, total serum IgE, skin prick test, specific IgE, and chest X-ray.

The mild T2 patient had normal spirometry and no bronchodilator reversibility when examined in autumn. The majority of the participants agreed that this did not exclude asthma as the patient was asymptomatic at the time. However, approximately 20% of the Allergy Doctors and 15% of the Respiratory and the Generalists were 'certain' about the diagnosis and would prescribe a reliever for use when needed (Table e1) [Note, this questionnaire was sent out in 2018, before the change in GINA guidelines recommending the maintenance and reliever therapy (MART) approach for mild asthma].

The majority of the participants across all groups agreed that the patient's asthma was uncontrolled (as per GINA classification)[17] when asthma status was reviewed during spring. Approximately 80% of the Allergy Doctors as opposed to 61.7% and 56.0% of the Respiratory and the Generalists respectively replied that the patient's phenotype was 'allergic asthma' ($p<0.0001$). As part of the same question, 30% of the Allergy Doctors (additionally) included the patient under 'T2 asthma' compared to 13.6% and 1.3% of the Respiratory and the Generalists ($p<0.0001$) (Table e1).

The majority of participants in all groups indicated that in addition to treatment for nasal symptoms, they would prescribe inhaled steroids and provide an asthma action plan. All asthma treatment options were similarly popular in the three groups except that half of the Allergy Doctors would commence the patient on allergen immunotherapy compared to 6.7% and 2.7% in the other groups ($p<0.0001$) (Table e4).

Severe T2 asthma:

Box 2.

Case vignette 2.

A 21 year-old male, BMI=23, comes for a consultation due to coughing, shortness of breath and wheezing. He has been suffering with asthma since childhood; from 3-12 years of age he was treated with inhaled budesonide, later on with fluticasone/salmeterol 50/250 dry powder inhaler, 1 puff twice-daily, while the last 4 years with fluticasone/salmeterol 50/500 dry powder inhaler, 1 puff twice-daily. Despite this treatment, he suffers from night symptoms twice a week which prompt him to use salbutamol. Playing football or cycling also cause asthma exacerbation especially during Spring. He complains of itchy eyes and nose, sneezing and runny nose all year round but worse during springtime. He uses loratadine on demand for his nasal and ocular symptoms.

He is a student in journalism, with no exposure to chemicals or other substances and doesn´t smoke. He lives in a house with a tree-garden in a small town, and does not keep pets.

In the patient with severe T2 asthma, spirometry with reversibility, FeNO, blood eosinophils, total IgE, skin prick test, specific IgE, and chest X-Ray were all statistically less popular among the Generalists than Specialists (Table 3).

The majority of participants agreed that the patient's asthma was uncontrolled (as per GINA Guidelines). Just 66% of the Generalists versus 91.9% of the Allergy and 76.4% of the Respiratory Doctors would evaluate the presence of comorbidities in order to manage this patient ($p<0.0001$). More than 80% of participants across all groups would evaluate patient's adherence and inhaler technique (Table e2).

Significantly more Allergy doctors regarded the patient's asthma type as 'allergic asthma' (71.7%) and/or T2 asthma (31.3%) than the other groups ($p=0.007$). Interestingly, a fifth of Generalists and one in ten Respiratory Doctors stated that they did not know the patient's asthma type ($p=0.001$). There was widespread agreement that the patient was at risk of acute attacks (Table e2).

Although only around two thirds of participants recognised uncontrolled rhinitis as a risk factor for asthma attacks, rhinitis treatment was the most popular option for asthma management, followed by montelukast. Significant differences were noted in terms of the third most popular treatment choice

which was tiotropium for the Respiratory Doctors (46.5%, p<0.0001) and allergen immunotherapy for the Allergy Doctors. (50.5%, p<0.0001) (Table e2).

The majority of participants would proceed with an asthma control test and/or a lung function with reversibility test at the patient's follow-up appointment. Fewer (53.2%) Generalists would use FeNO to investigate asthma control compared to Allergy (73.7%) and Respiratory Doctors (69.5%) (p=0.04). If asthma control was not achieved, 40% of Generalists would refer the patient to an asthma clinic while most of the Allergy and Respiratory Doctors would start the patient on omalizumab (Table e2).

Survey 2: Non T2 asthma

Box 3.

Case vignette 3.

A 50 year-old lady attends as an emergency due to breathlessness. She reports that her dyspnea has worsened over the last two weeks despite using 2 puffs of beclomethasone dipropionate/formoterol (100/6 μg) twice daily and that she now needs to use her reliever (salbutamol) four times a day. On presentation, she talks in phrases but wheezes, her oxygen saturation is 92%, pulse rate at 118bpm, respiratory rate at 28bpm, FEV1 72% pred., FVC 82% pred., FEV1/FVC 0.68 while electrocardiography is unremarkable. She was diagnosed with asthma 10 years ago (PC20 for methacholine <4 mg/ml), skin prick testing to common aeroallergens was negative. Since then she has been on high doses of inhaled corticosteroids but often uses salbutamol after exercise and sometimes during the night. She has to take oral corticosteroids around 4 times a year for asthma exacerbations and was hospitalized due to asthma twice in the last 5 years (once at ICU). She is 160 cm tall, weighs 90 kg, works in a dye-factory and has been occasionally smoking the last 30 years.

Follow-up information:

- Spirometry results are as following: FEV1 79% pred., FVC 82% pred., FEV1/FVC 0.72, reversibility 7% (150ml). Chest auscultation normal. She still needs to use her reliever at least three times a week.
- FeNO is 6 ppb. Skin prick testing with common aeroallergens is negative. Blood eosinophils 48/cml.

The majority (49.9%) of the 677 participants were Respiratory Doctors as opposed to 30.3% and 19.8% who were Allergy Doctors and Generalists respectively (Table 2). Most (45%) worked in tertiary care, while approximately 26% and 29% were working in secondary and primary care, respectively.

Deciding on emergency management was challenging for all groups and there were statistically significant differences in how much prednisolone should be prescribed (Table e3). At follow-up, the priority for all groups was to ensure that inhaler technique was correct. Of note, less than two-thirds of the participants across all groups considered evaluating for occupational exposure in this patient who worked in a dye factory (Table 3).

The majority of the participants agreed that the patient's asthma was uncontrolled and most considered that the patient's asthma phenotype was obesity-related (p=0.006) while a significantly higher percentage (19%) of the Respiratory Doctors classified the patient's asthma as T2 compared to the other specialties (p=0.002). Tiotropium (p=0.02) and education (p=0.96) were the most popular answers regarding the loptimal ong-term management of this patient. Allergy Doctors were more likely to consider anti-IL5 (p<0.0001) or anti-IgE (p=0.008) treatment (Table e3).

Fewer Generalists prioritized the assessment of comorbidities (p=0.049), adherence (p=0.01) and inhalation technique (p=0.05) compared to the other two groups. Smoking cessation was prioritised by all groups but pulmonary rehabilitation was chosen more often by Respiratory and Generalists than Allergy Doctors (Table e3).

Systematic review results (Aims 2 and 3)

Details of the search and selection process are summarised in a PRISMA flowchart (figure 1). Our search yielded 3,722 unique titles, of which 52 studies evaluated strategies aimed at improving adherence to guidelines on diagnosis, assessment and/or long-term management of asthma, while 24 evaluated adherence to guideline recommendations on the assessment and management of acute asthma attacks. Differences in the care provided and asthma-related outcomes of patients managed by a specialist (respiratory physician or allergist), or a generalist (internist or general practitioner) were evaluated in 16 studies, of which 13 focused on long-term asthma management and three on acute attacks.

Risk of bias

Most studies evaluating strategies to improve implementation of guideline recommendations were at high/serious risk of bias (tables e4~~, e5~~). Entirely appropriately, given that the implementation

strategies were targeted at improving guideline adherence by clinical teams, all the included interventional trials were cluster randomised and therefore potentially at risk of selection and detection bias. Moreover, several trials did not evaluate asthma-related outcomes and it was not always clear if this represented reporting bias. Moderate or serious risk of bias was also identified for most observational studies, due to confounding, participant selection, and often outcome selection as well. Only one longitudinal evaluation of the primary care practices in Bavaria was deemed to be at low risk of bias (Table e45).

High risk of methodological bias was identified in all 16 studies comparing care provision by Specialists and generalists apart from two observational studies that were deemed of low risk (table e46). The two RCTs were at high risk of selection and detection bias, while there were concerns regarding unaddressed confounding for most of the included observational studies (specifically confounding because Specialists tended to care for patients with more severe/ uncontrolled asthma, and more severe acute attacks than Generalists).

Strategies to improve adherence to guideline recommendations for long-term management of asthma. (Aim 2)

We identified 27 RCTs or cluster RCTs, 19 before-after studies, and six parallel comparative cohort studies, evaluating strategies for improving adherence to asthma guidelines (figure 2, tables 4, e54). All but three studies were conducted in primary care settings. Specific interventions included the provision of additional clinical input by a specialist HCP (usually a specialist nurse or pharmacist, 13 studies)[29,30,31,32,33,34,35,36,37,38,39,40], medical education (12)[41,42,43,44,45,46,47,48,49,50,51,52], computer decision-support systems (7)[53,54,55,56,57,58,59], introduction of asthma care pathways (4)[60,61,62,63], new local or national guideline (4)[64,65,66,67], or the participation of the centre in asthma-related clinical trials (1)[68]. Multifaceted quality improvement implementation strategies were evaluated in 11 studies[51,69,70,71,72,73,74,75,76,77,78,79].

Process outcomes were evaluated in most studies (46/52, 88.5%), of which 33 (71.7%) demonstrated improved adherence to guideline recommendations. The impact on asthma-related outcomes was evaluated in 31/52 (59.6%) studies. Only 18/31 (58.1%) showed any clinical benefit. Of note, this evaluation included the only observational study at low risk of bias, a large (n=109,042 patients) multifaceted quality improvement initiative conducted in Bavarian primary care[73].

Findings stratified by the type of intervention are summarized in figure 2 and table e54. The introduction of additional specialised HCPs support for patient care (such as a respiratory trained nurse or a pharmacist) into the primary setting was evaluated in 13 studies including large cluster RCTs

of high risk of bias and observational studies that were deemed at moderate risk of bias. Most studies demonstrated improvement in process outcomes and many also demonstrated clinical benefits.

Multifaceted quality improvement projects were assessed by 11 studies including three cluster RCTs, that were of high risk of bias, and several before-after studies, including four that were deemed low or moderate risk of methodological bias. Process and clinical benefits were demonstrated in most cases, including all the low and moderate risk of bias studies. However, it should be noted that two of the three cluster RCTs did not show process benefits and the only RCT evaluating clinical outcomes did not demonstrate any benefit either.

A number of studies evaluated specific strategies for improving guideline adherence such as computer decision-support systems, medical education, asthma care pathways with some promising results though typically in studies which combined several interventions. For example, introduction of an asthma care pathway or computer decision support system were more effective when paired with an educational component. The introduction of new guidelines with or without a training component appeared the least effective method for improving adherence. Use of interactive and case-based learning methods appeared more effective than simple lectures or printed training material.

Strategies to improve adherence to guidelines on the assessment and management of acute asthma attacks (Aim 2)

Three of the eligible studies were cluster RCTs, 17 were before-after and four were comparative cohort studies with concurrent and/or historical controls (Figure 3, Tables 1, E62). Three of the included studies were conducted in primary care, while the remainder were conducted in a hospital setting (mostly in emergency departments). Specific interventions included the introduction of acute asthma care pathways (n=12)[80,81,82,83,84,85,86,87,88,89,90,91], of additional patient specific input by a specialised health professional (1)[92], of a computer decision support system (1)[93], or of a national clinical guideline (1)[94], or the provision of medical education (1)[52]. Nine studies (including the two RCTs) evaluated multi-faceted quality improvement initiatives[95,96,97,98,99,100,101,102,103].

Process outcomes were evaluated in all but one study (23/24, 95.8%), and 18/23 (78.3%) showed a beneficial impact on adherence to treatment recommendations. Clinical outcomes were evaluated in 11 (45.8%) studies, and a clinical benefit was evident in only 3 of them (27.3%).

Acute asthma care pathways were evaluated in eight observational studies. All were deemed high risk of bias except for two that were moderate. Overall, asthma care pathways appeared effective in improving process but not clinical outcomes. Multifaceted quality improvement processes, evaluated

in two cluster RCTs and six observational studies, including two that were at moderate risk of bias, showed beneficial effect on process, and possibly on clinical outcomes. Data about the clinical effectiveness of other interventions were not reported.

Differences in process and clinical outcomes of patients managed by a specialist or a generalist (Aim 3)

Diagnosis, assessment and/or management of long-term asthma by Specialists (respiratory physicians or allergists) compared to Generalists (general physicians or general practitioners) was evaluated in two RCTs (both at high risk-of-bias) totalling 617 participants[104,105], and 14 observational studies, including six large studies using routine health databases (three cross-sectional and three longitudinal studies)[106,107,108,109,110,111], and smaller cross-sectional studies, including audits (figure 4, table e76)[112,113,114,115,116]. Management of acute asthma attacks was evaluated in three audits, totalling 1,838 participants[117,118,119].

Adherence to guideline recommendations was evaluated in 10/12 studies, showing significantly better adherence by Specialists, both for long-term asthma management and acute asthma attacks. Four of five studies showed that Specialists' care was associated with improved clinical outcomes including one cross-sectional study at low risk-of-bias which demonstrated differences in specialist/general practitioner diagnosis.

DISCUSSION

Summary and interpretation of results

Aim 1: Adherence to international asthma guidelines by HCPs of different specialties

The three online questionnaires gathered a good sample of approximately 1,500 international participations in total spanning primary, secondary and tertiary care. These diverse settings clearly influenced responses despite participants being advised that they had access to all diagnostic and management facilities. For example, diagnostically, Generalists favoured serial home peak flows to test for flow variability, whereas Respiratory and Allergy doctors would request FeNO which reflects familiarity and the context of their practice. Similarly, Allergy doctors were confident in identifying T2 and non-T2 phenotypes, a distinction which appeared to have little relevance for Respiratory doctors or Generalists, despite the increasing recognition of disease heterogeneity[120]. However, possible differences in the terminology used across the respondents' group may also be the cause of

the latter observation; characteristically, the terms used in severe asthma guidelines are eosinophilic and non-eosinophilic asthma[121,122].

Guidelines recognise both the importance of assessing characteristic symptom patterns and undertaking objective tests in order to make a diagnosis of asthma[17,18]. The poor sensitivity and specificity of many investigations[17,18] was reflected in the 'certainty' with which participants (in all groups) diagnosed the mild T2 patient as having asthma and offering treatment despite normal spirometry and no significant bronchodilator reversibility. Concerningly, in the severe cases, far from all participants would check the patient for comorbidities (ranging from 66% to 93.4%).

There was general agreement on core management strategies (role of intranasal corticosteroids, action plans, checking inhaler technique and adherence, supporting smoking cessation, treatment of nasal symptoms) but the clinical context of respondents influenced selection of other treatment modalities. For example, Allergy doctors prioritised immunotherapy or biologicals, while tiotropium and pulmonary rehabilitation was chosen more often by Respiratory doctors and Generalists. The importance of oral steroids in an acute attack was not in doubt, but the dosages chosen varied considerably (from 1mg/kg to 1mg/kg/day and 50mg prednisolone). GINA guidelines currently recommend for adults 1mg/kg/day and up to 50mg/day of prednisolone or equivalent for 5-7 days[17].

GINA highlights the need to adapt asthma management strategies to enable implementation within local/national healthcare settings[17]. Whilst some of the discrepancies identified in our survey may be due to poor dissemination or lack of knowledge, a considerable proportion of the diverse responses from Allergy/Respiratory doctors and Generalists are likely to reflect adaptations consistent with their different clinical settings. Effective implementation strategies are considered in the evidence from the systematic reviews.

Aim 2: Effectiveness of strategies to improve implementation of guideline-recommended interventions

Our systematic reviews evaluated various strategies for improving implementation of asthma guidelines. The strategies were grouped into broad categories, however inconsistencies were observed in the results of studies evaluating strategies in each category, complicating interpretation. The main sources of heterogeneity were differences in the characteristics of individual interventions, in the methods for delivering the intervention (e.g. engagement and training of the clinical staff), the context in which the interventions were delivered and the outcomes assessed.

Patient-specific input by additional specialized health professionals was evaluated in 13 studies, including large cluster RCTs of high risk of bias and observational studies that were deemed at

moderate risk of bias. The vast majority of studies evaluating this intervention demonstrated improved process outcomes and most also demonstrated clinical benefits. However, cost-effectiveness of this approach has not been evaluated, and it is not clear if this benefit is sustained after the trial is completed in case the additional support is withdrawn. In contrast, a large-scale cluster RCT in which existing primary care staff were upskilled was not effective[37].

Multicomponent quality improvement initiatives incorporating a range of implementation strategies addressing multiple challenges to guideline adherence (such as training health professionals, on-going audit and feedback/benchmarking, introduction of asthma care pathways, identification and resolution of organisational barriers[123]) appeared the most effective. Characteristically, the strategies employed in the three studies that did not show improved outcomes (either clinical or process) only included two components; audit and feedback to clinicians. Similarly, findings from studies evaluating a single intervention were in general less consistent. Multifaceted quality improvement projects incorporating a range of implementation strategies addressing challenges to guideline adherence at the level of the patient, health professional and health system were more likely to be effective. This reflects recognition of the need to take a whole systems' approach to improving practice[124,125].

Asthma care pathways were mostly evaluated in high-risk of bias studies, which however showed clinical and process benefits. Studies evaluating other interventions were mostly at high risk of bias and their findings were either inconsistent (computer decision-support systems, medical education), or negative (introduction of a guideline, participation in clinical trials).

Some studies with longer observation periods[97,103] noted that the impact of the interventions tended to wane and needed continuous reinforcement, for example through audit, feedback and re-training.

Strategies for improving adherence to guidelines have been evaluated in previous systematic reviews, with consistent findings. Two systematic reviews assessing a broad range of strategies concluded that multifaceted quality improvement programmes were more effective than single component interventions, especially those based explicitly on a theoretical framework, with a strong educational component including a combination of instructional modalities, longer duration[126], and those promoting engagement at the level of the patient, health professionals and organisation[127]. Other systematic reviews focusing on specific approaches concluded that input by pharmacists[128] and asthma care protocols[129] could be beneficial, while medical education[130] and computer decision support systems[131] were not effective, though it was not clear whether limitations of the interventions or implementation methods were responsible for this lack of observed benefit.

Aim 3: Comparison of process and clinical outcomes in patients managed by Specialists or Generalists

This systematic review was informed by fewer studies, most of which were observational and at high risk of bias. Almost all studies showed that specialist care was associated with better adherence to guideline recommendations, with some suggestion in six of the seven studies evaluating clinical outcomes these may also be improved. It should be noted that specific findings from some of the older studies' may no longer be applicable. For example, two of these studies date from the early days of ICS prescribing when Generalists may have been more cautious[105,110]. Improved diagnosis by Specialists in a cross-sectional study at low risk of bias, might reflect better access to investigations[119]. However, Specialists care was consistently associated with better outcomes in more recent studies. It should also be highlighted that only one extensive observational study evaluating process outcomes and a smaller observational study evaluating clinical outcomes were low risk of bias, with the remaining being deemed high risk.

Asthma diagnosis, assessment and management are complex and the respective guidelines are updated frequently, making it more challenging for the generalist to keep updated. Robust, continuous, multifaceted quality improvement projects will be required to ensure that patients receive high-quality care with locally agreed referral pathways for specialists' advice.

Strengths and limitations

The survey results provided an insight into asthma management at international level with a good number of responses from across all levels of care. A limitation to our results is that the second survey participants were not asked whether they had also taken part in the first survey, hence we cannot be sure of the total number of unique participants. Furthermore, the setup of the surveys did not facilitate analysis of the results according to the country in which the participants practised and, we are unable to establish whether variations in the answers received may have been country-related. Finally, a higher proportion of the participants were respiratory physicians. However, all surveys included adequate responses from allergists and generalists, that allowed the panel to derive informed conclusions.

Our systematic reviews have a number of limitations. The study protocol was not made publicly available, however, it was developed prospectively and submitted to the ERS and EAACI. Most of the included studies were at high risk of bias, which reduces the confidence in the findings. Most included trials were cluster RCTs. Although this is the optimal study design for evaluating implementation targeted at clinical teams, they are at high risk of selection, performance and detection bias based on

the Cochrane risk of bias tool. Confounding was the main source of bias in observational studies and despite several studies accounting for confounding factors, adjustments were not deemed adequate in most cases. In the systematic review comparing the outcomes of patients evaluated by Specialists versus Generalists, a key confounder was that Specialists tend to care for people with more severe or uncontrolled asthma. Better outcomes among these patients could either reflect better quality of care provided by Specialists, or that there was greater capacity for improvement. We were not able to conduct meta-analyses, due to the considerable clinical and methodological heterogeneity, but our results are presented in detail, both tabulated and illustrated in harvest plots to facilitate interpretation.

Last, but not least there is significant heterogeneity among the current international asthma guidelines, thus this might be reflected in the interventions meant to improve adherence.

Implications for practice and research

Asthma is a heterogeneous disease, meaning that its diagnosis, assessment and management are complex[17,18]. In parallel, it is the focus of intensive research that leads to continuous change to clinical practice guidelines and practice, increasingly incorporating precision medicine interventions[22],[132]. As a result, implementation of asthma guidelines and delivery of high-quality, evidence-based medicine is challenging and often suboptimal[133,134,135]. Our findings suggest that continuous multifaceted quality improvement processes can enhance adherence to guidelines. Additional input by a Specialist, either a Respiratory Physician, Allergist, or a respiratory trained nurse or pharmacist, also appears to improve guidelines adherence and clinical outcomes, although further data is needed to confirm sustainability of these findings. Moreover, the feasibility and cost-effectiveness of these approaches should be evaluated.

Our survey revealed significant variability in practice, across different clinical settings, that reflects guideline adaptations in a real-life context, where different diagnostic or therapeutic options and sources are available. Guideline panels need to consider these practical differences when developing clinical recommendations, and to offer options for evidence-based practice in different clinical settings.

Systematic literature review also indicated a potential association of specialist care with improved process and clinical outcomes. However, more data are needed, as confidence was limited on this finding. Undoubtedly, the complexity of asthma care imposes the need for a multidisciplinary approach to the diagnosis and management of these patients. As a result, it is now widely

recommended that patients with severe asthma should be managed in specialised severe asthma clinics[11,17,18,121,122]. However, the diagnosis and management of patients without severe asthma is also complex, but it is still unclear when generalist or specialist care is necessary[11,17,18,121,122]. This complicates the work of both generalists and specialists, and -as suggested by our SR- may also impact on the clinical outcomes of individuals with asthma. Therefore, data are needed to inform standardization in the indications for referral of patients for specialist review, that should be tailored to the balance of resources required for continuous multifaceted quality improvement processes in primary care versus the evaluation of an increased proportion of individuals with asthma in specialty clinics. In the meantime, locally agreed referral pathways to specialists are crucial both for Generalists and for Specialists from different disciplines who have different approaches to diagnostic uncertainty and managing patients with poorly controlled asthma.

The emergence of the Coronavirus Disease 2019 (COVID-19) has extensively affected the care of people with asthma, mainly by replacing physical appointments with virtual encounters, while in parallel reinforcing telemonitoring technologies[136,137]. It is recognized that to some extent these practice changes introduced during 2020 will outlive the pandemic, as they appear effective, convenient for patients and require fewer resources[138,139,140,141,142,143]. An opportunity emerges to use these new technologies to enhance adherence to guidelines. For example, efficient methods for capturing disease characteristics in a computer-usable format could facilitate patient profiling and strengthen decision support systems. Such interventions are already being evaluated in other disease areas with promising preliminary results[144,145].

Box 4: Key messages

- Implementation of guidelines is different across different asthma management settings.
- Guideline recommendations need to account for differences in resource availability across the various asthma care settings, including primary care.
- Continuous multifaceted quality improvement processes can improve guidelines adherence.
- Additional input from specialised health professionals could also be effective towards improving guidelines adherence. However, this is unlikely to be sustainable unless long-term funding is available.
- Locally agreed referral pathways to specialists are crucial both for Generalists and Specialists from different disciplines who have different approaches to diagnostic uncertainty and managing patients with poorly controlled asthma.
- More data are needed to evaluate differences in process and clinical outcomes among patients managed by Generalists or Specialists and to facilitate standardization in the indications for referral of patients for specialist review.

CONCLUSION

This evaluation conducted as a joint initiative between EAACI and ERS showed a significant gap in implementing asthma guidelines in real life. This calls for action on several fronts: a) guideline developers should consider the heterogeneity of settings for asthma management in real life and tailor their recommendations accordingly; b) multifaceted interventions should receive better funding to improve adherence to guidelines; c) validated referral pathways for uncontrolled asthma or for uncertain diagnosis should be prioritized.

Tables and figures:

Table 1. Systematic review questions. **A.** SR-1: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and long-term management of asthma. **B.** SR-2: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and management of acute attacks. **C.** SR-3: Process and clinical outcomes in patients managed by Specialists or Generalists.

Table 2. Health care profession and subsequent categorisation in the analyses of the survey.

Table 3. Preferred diagnostic procedure in different subtypes of asthma, as reported in the online survey. *P-values pertain to comparisons among the three groups, using chi-squared test.

Table 4. Types of studies evaluating the adherence to asthma guidelines and the proportion of studies demonstrating beneficial (a) clinical and (b) adherence outcomes, among the studies evaluating such outcomes.

Figure 1. PRISMA flow diagram.

Figure 2. Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for asthma assessment and maintenance management.

Figure 3. Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for acute asthma attacks assessment and management.

Figure 4. Harvest plot summarizing the findings of studies evaluating differences in the adherence to asthma guidelines by Specialists or Generalists.

Table 1. Systematic review questions.

A. SR-1: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and long-term management of asthma.

Population	Patients with a clinical diagnosis of asthma. Patients with a clinical suspicion of asthma, for studies evaluating asthma diagnosis.
Intervention	Interventions aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and long-term management of asthma.
Comparator	Any other intervention aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and long-term management of asthma, or no intervention
Outcomes	Clinical outcomes such as frequency of acute attacks, episodes of hospitalisation, asthma symptoms, or quality of life. Process outcomes, such as adherence to specific guidelines components (e.g. prescription of inhaled corticosteroids for patients requiring maintenance treatment, or delivery of smoking cessation advice).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.

B. SR-2: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and management of acute attacks.

Population	Patients with a clinical diagnosis of an acute asthma attach. Patients with a clinical suspicion of acute asthma attach, for studies evaluating asthma attack diagnosis.
Intervention	Interventions aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and management of acute asthma.
Comparator	Any other intervention aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and management of acute asthma, or no intervention
Outcomes	Clinical outcomes such as need for hospital admission, duration of symptoms, treatment success or failure, need for intubation or mechanical ventilation. Process outcomes, such as adherence to specific

	guidelines components (e.g. prescription of oral corticosteroids for all patients with an acute attack leading to an emergency presentation or hospital admission).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.

C. SR-3: Process and clinical outcomes in patients managed by Specialists or Generalists.

Population	Patients with a clinical diagnosis of asthma or acute asthma attack. Patients with a clinical suspicion of asthma or acute asthma attack, for studies evaluating asthma or acute asthma attack diagnosis, respectively.
Exposure A	Management by an asthma specialist (respiratory physician or allergist).
Exposure B	Management by a generalist (general practitioner or internist, not specialised in asthma).
Outcomes	For studies evaluating the diagnosis, assessment or long-term management of asthma: Clinical outcomes such as frequency of acute attacks, episodes of hospitalisation, asthma symptoms, or quality of life. Process outcomes, such as adherence to specific guidelines components (e.g. prescription of inhaled corticosteroids for patients requiring maintenance treatment, or delivery of smoking cessation advice). For studies evaluating the diagnosis, assessment or management of acute asthma attacks: Clinical outcomes such as need for hospital admission, duration of symptoms, treatment success or failure, need for intubation or mechanical ventilation. Process outcomes, such as adherence to specific guidelines components (e.g. prescription of oral corticosteroids for all patients with an acute attack leading to an emergency presentation or hospital admission).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.

Table 2. Health care profession/level of training and subsequent categorisation in the analyses of the survey

Category	n (%)	Categories in the analyses
1st Survey: Mild T2 & Severe T2 asthma		
Allergy – Asthma specialist	22 (2.5)	Allergy doctor
Allergy specialist	133 (15.2)	Allergy doctor
Trainee in Allergy	9 (1.0)	Allergy doctor
Respiratory – Asthma specialist	123 (14.1)	Respiratory doctor
Respiratory doctors	456 (52.1)	Respiratory doctor
Trainee in Respiratory Medicine	34 (3.9)	Respiratory doctor
General Practitioner	48 (5.5)	Generalist
Internist	28 (3.2)	Generalist
Specialist nurse	13 (1.5)	Generalist
Trainee General Practitioner	4 (0.5)	Generalist
Trainee in Internal Medicine	4 (0.5)	Generalist
Nurse trainee	1 (0.1)	Generalist
2nd Survey: non T2 asthma		
Allergy – Asthma specialist	30 (4.4)	Allergy doctor
Allergy specialist	163 (24.0)	Allergy doctor
Trainee in Allergy	12 (1.8)	Allergy doctor
Respiratory – Asthma specialist	80 (11.8)	Respiratory doctor
Respiratory doctors	245 (36.1)	Respiratory doctor
Trainee in Respiratory Medicine	13 (1.9)	Respiratory doctor
General Practitioner	99 (14.6)	Generalist
Internist	16 (2.4)	Generalist
Specialist nurse	14 (2.1)	Generalist
Trainee General Practitioner	4 (0.6)	Generalist
Trainee in Internal Medicine	2 (0.3)	Generalist
Nurse trainee	1 (0.2)	Generalist

Table 3. Preferred diagnostic procedure in different subtypes of asthma as reported in the online survey. *P-values pertain to comparisons among the three groups, using chi-squared test.

	Allergy doctors (%)	Respiratory doctors (%)	Generalists (%)	P-value*
Mild T2 asthma				
Spirometry with reversibility test	95.0	96.4	86.9	0.001
Peak flow	24.1	27.8	39.3	0.04
FeNO	49.0	58.7	41.7	<0.0001
Blood Eosinophils	57.2	73.7	63.1	<0.0001
Total IgE	49.7	63.6	41.7	0.006
Skin prick test	93.1	65.4	50.0	<0.0001
Specific IgE	53.1	38.0	32.1	0.001
Chest X-ray	36.6	55.7	23.8	<0.0001
ENT examination	31.7	31.4	29.8	0.95
Bronchoscopy	0	2.5	1.2	0.12
Bronchial provocation	19.3	31.9	20.2	0.002
Bacterial culture	4.1	7.4	7.1	0.38
Detailed history	70.3	68.1	66.7	0.82
Chest auscultation	55.9	48.3	41.7	0.10
Serial peak flow	53.1	62.9	75.0	0.004
Severe T2 asthma				
Spirometry with reversibility test	98.0	96.4	85.1	0.001
Peak flow	19.2	24.1	25.5	0.55
FeNO	74.8	79.9	48.9	0.004
Blood Eosinophils	79.8	85.9	68.1	0.006
Total IgE	60.6	77.6	36.2	<0.0001
Skin prick test	99.0	78.4	57.4	<0.0001
Specific IgE	55.6	41.0	34.0	0.01
Chest X-ray	39.4	59.8	27.7	<0.0001
ENT examination	40.4	34.6	27.7	0.30
Bronchoscopy	1.0	1.7	2.1	0.86
Bronchial provocation	8.0	10.8	4.3	0.30
Bacterial culture	9.1	8.6	8.5	0.99
Detailed history	78.8	79.5	80.8	0.96
Chest auscultation	83.8	81.7	76.6	0.57
Serial peak flow	37.4	41.3	48.9	0.42
Check prescriptions	76.8	85.3	83.0	0.13
Assess inhalation technique	92.9	91.7	85.1	0.26

Non-T2 asthma				
Spirometry with reversibility test	65.4	69.5	49.2	<0.0001
Peak flow	14.6	21.0	28.4	0.009
FeNO	50.2	49.7	26.9	<0.0001
Blood Eosinophils	53.2	61.2	38.1	<0.0001
Total IgE	44.9	479	19.4	<0.0001
Skin prick test	26.3	14.2	9.0	<0.0001
Specific IgE	22.4	25.2	11.9	0.007
Chest X-ray	49.30	55.9	30.6	<0.0001
ENT examination	30.2	23.1	11.2	<0.0001
Bronchoscopy	1.5	3.2	2.2	0.42
Bronchial provocation	1.5	4.1	2.2	0.17
Bacterial culture	17..1	17.8	4.5	0.001
Detailed history	65.8	67.8	53.7	0.01
Chest auscultation	68.8	71.2	61.2	0.12
Occupational evaluation	55.1	66.3	56.0	0.02
Check adherence	66.3	71.0	59.7	0.06
Assess inhaler technique	72.2	79.9	64.9	0.002

Table 4. Types of studies evaluating the adherence to asthma guidelines and the proportion of studies demonstrating beneficial (a) clinical and (b) adherence outcomes, among the studies evaluating such outcomes.

	N	RCTs	Before-after	Comparative observational study	Beneficial clinical outcomes	Beneficial process outcomes
Assessment and management of asthma during stable disease state						
Additional patient specific input by a specialised health professional	13	8	2	3	8/12 (66.7%)	10/11 (90.9%)
Asthma care pathway	4	1	3		2/2 (100%)	3/3 (100%)
Computer decision-support systems	7	6	1		3/5 (60%)	4/7 (57.1%)
Introduction of a local or national guideline	4	2	1	1	0/1 (0%)	2/4 (50%)
Medical education	12	7	5		1/4 (25%)	5/10 (50%)
Quality improvement process	11	3	7	1	4/6 (66.7%)	8/10 (80%)
Participation in a clinical trial	1			1	0/1 (0%)	0/1 (0%)
Assessment and management of acute asthma attacks						
Acute asthma care pathway	12		11	1	1/8 (12.5%)	10/12 (83.3%)
Additional patient specific input by a specialised health professional	1			1	0/0 (N/A)	1/1 (100%)
Computer decision-support systems	1		1		0/0 (N/A)	1/1 (100%)
Introduction of a local or national guideline	1		1		0/0 (N/A)	0/1 (0%)
Medical education	1	1			0/0 (N/A)	0/1 (0%)
Quality improvement process	9	2	5	2	2/3 (66.7%)	6/7 (85.7%)

Figure 1. PRISMA Flow diagram

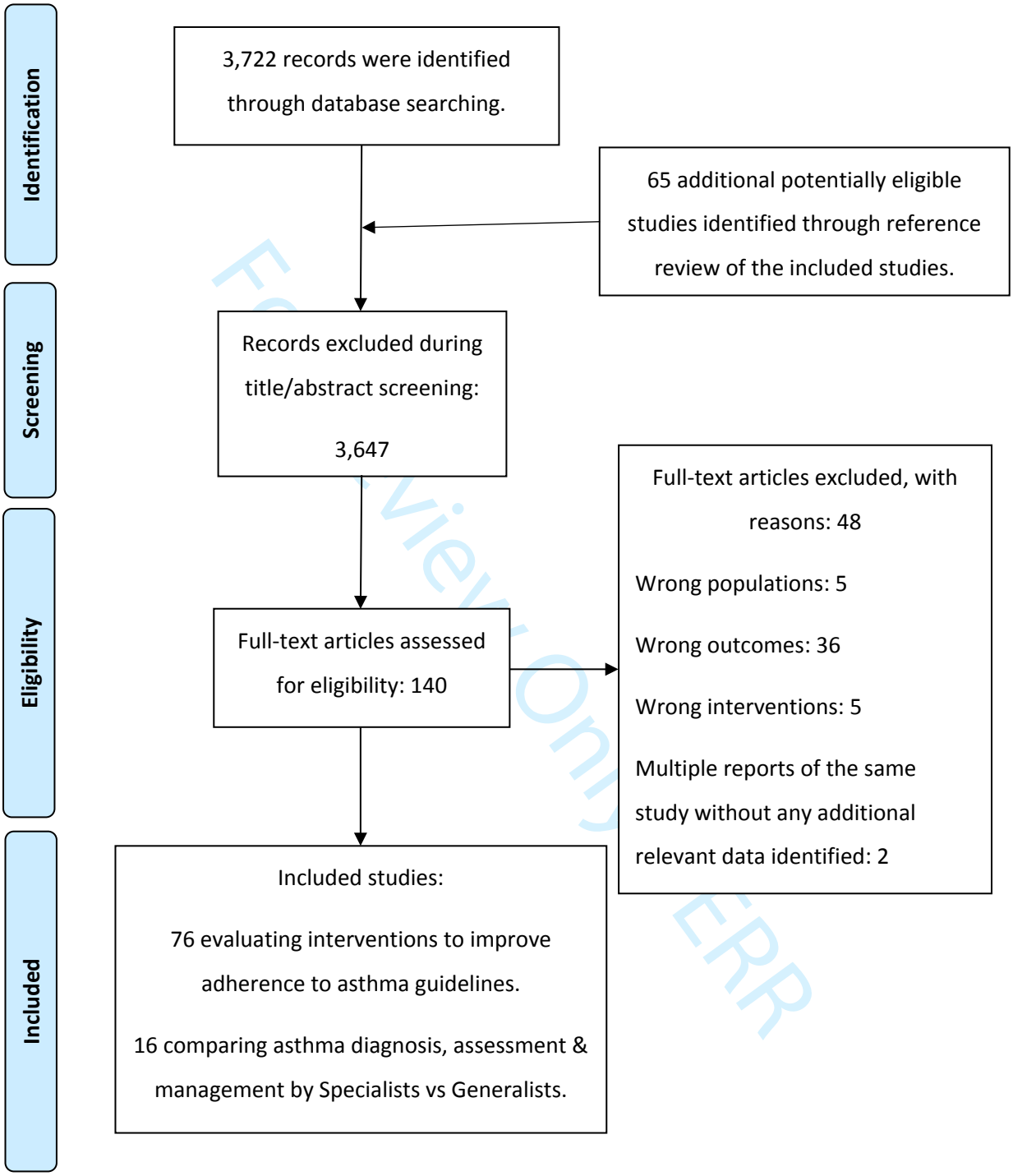


Figure 2. Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for asthma assessment and maintenance management.

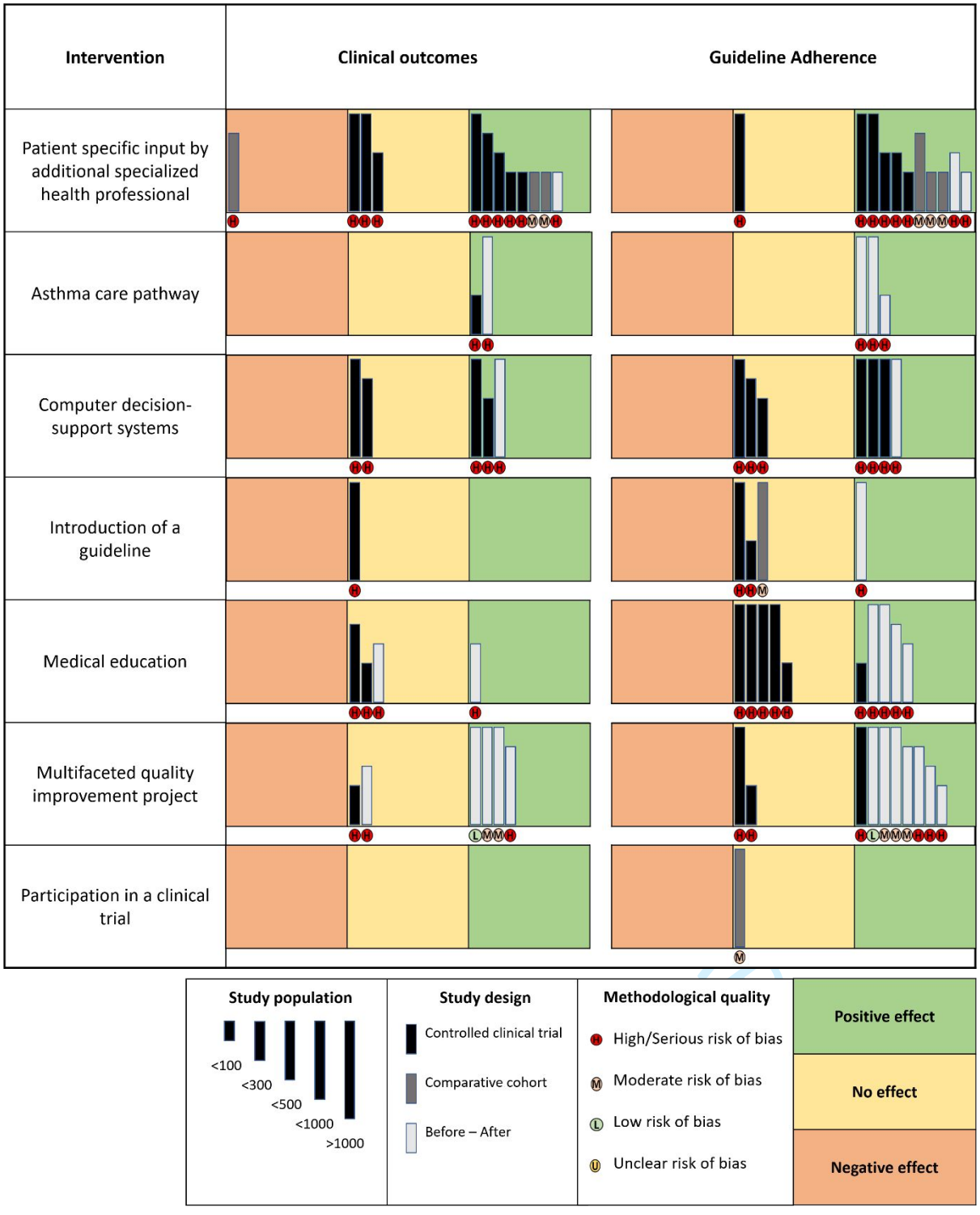


Figure 3. Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for acute asthma attacks assessment and management.

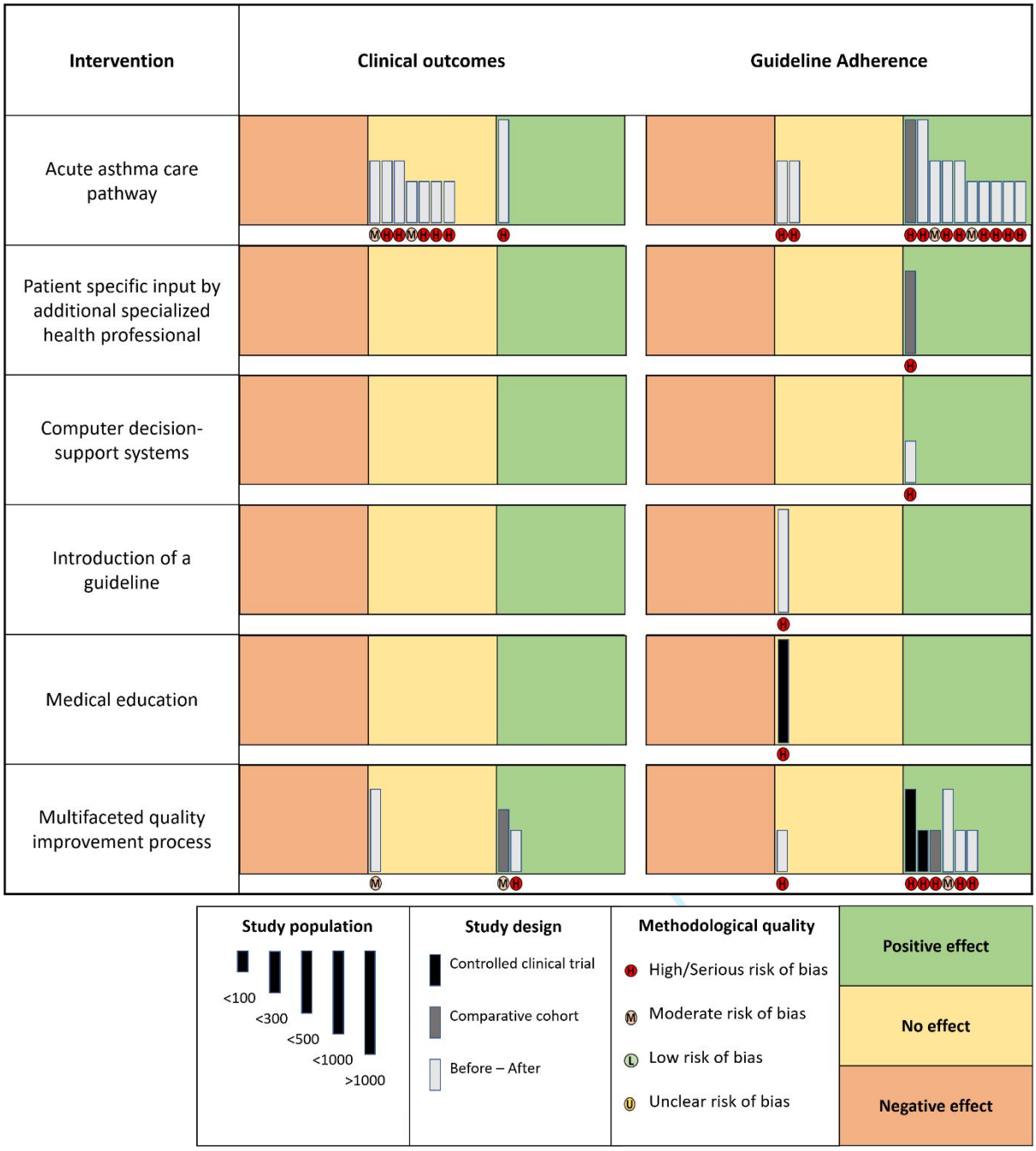
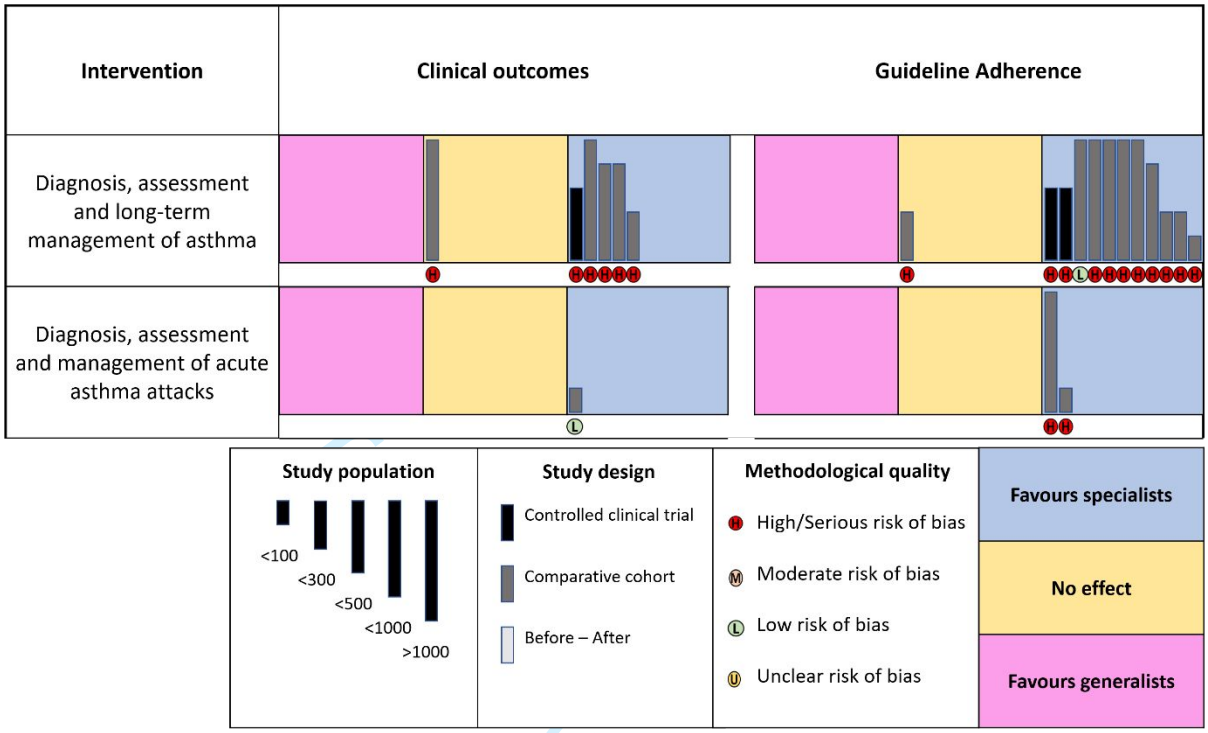


Figure 4. Harvest plot summarizing the findings of studies evaluating differences in the adherence to asthma guidelines by Specialists or Generalists.



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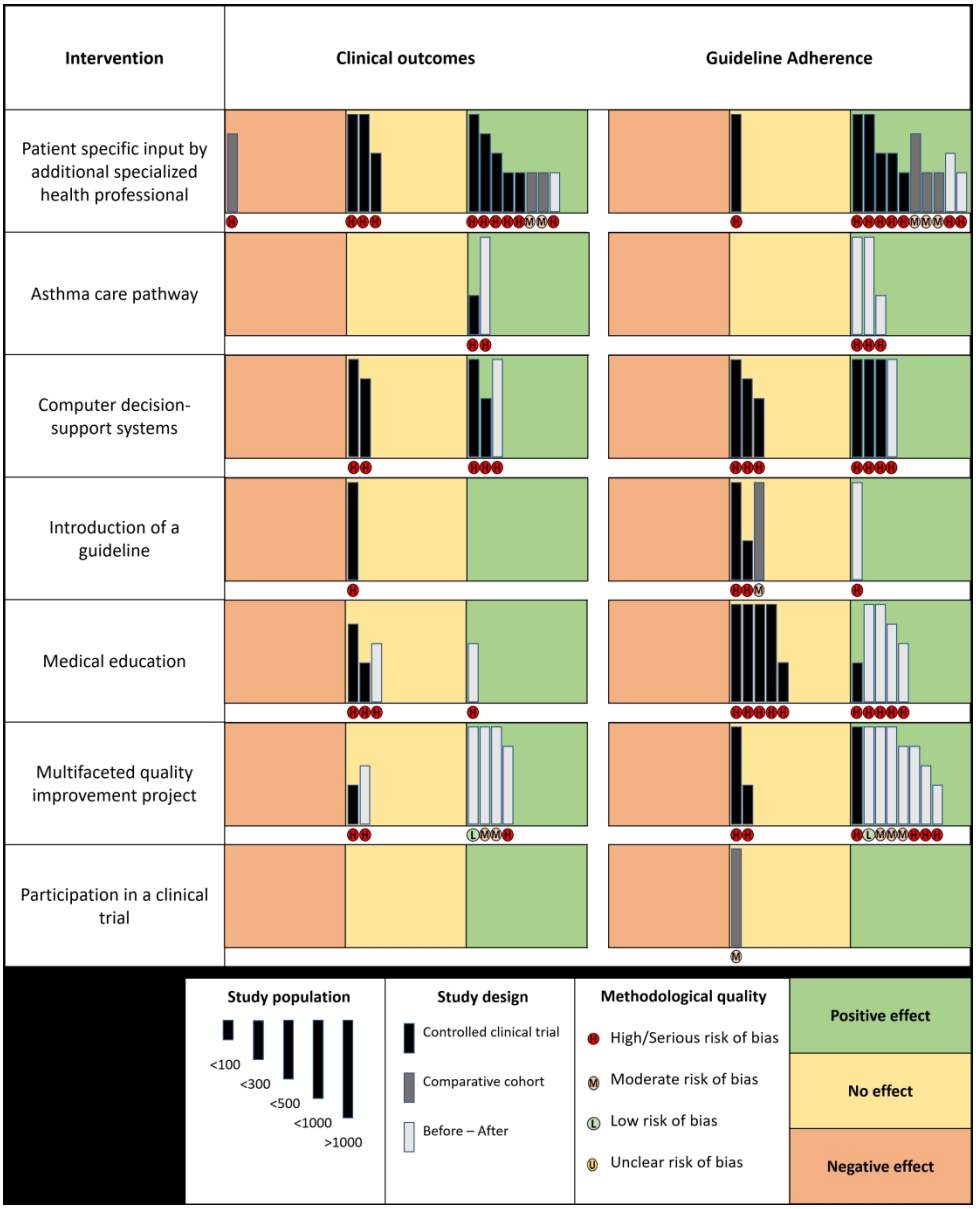
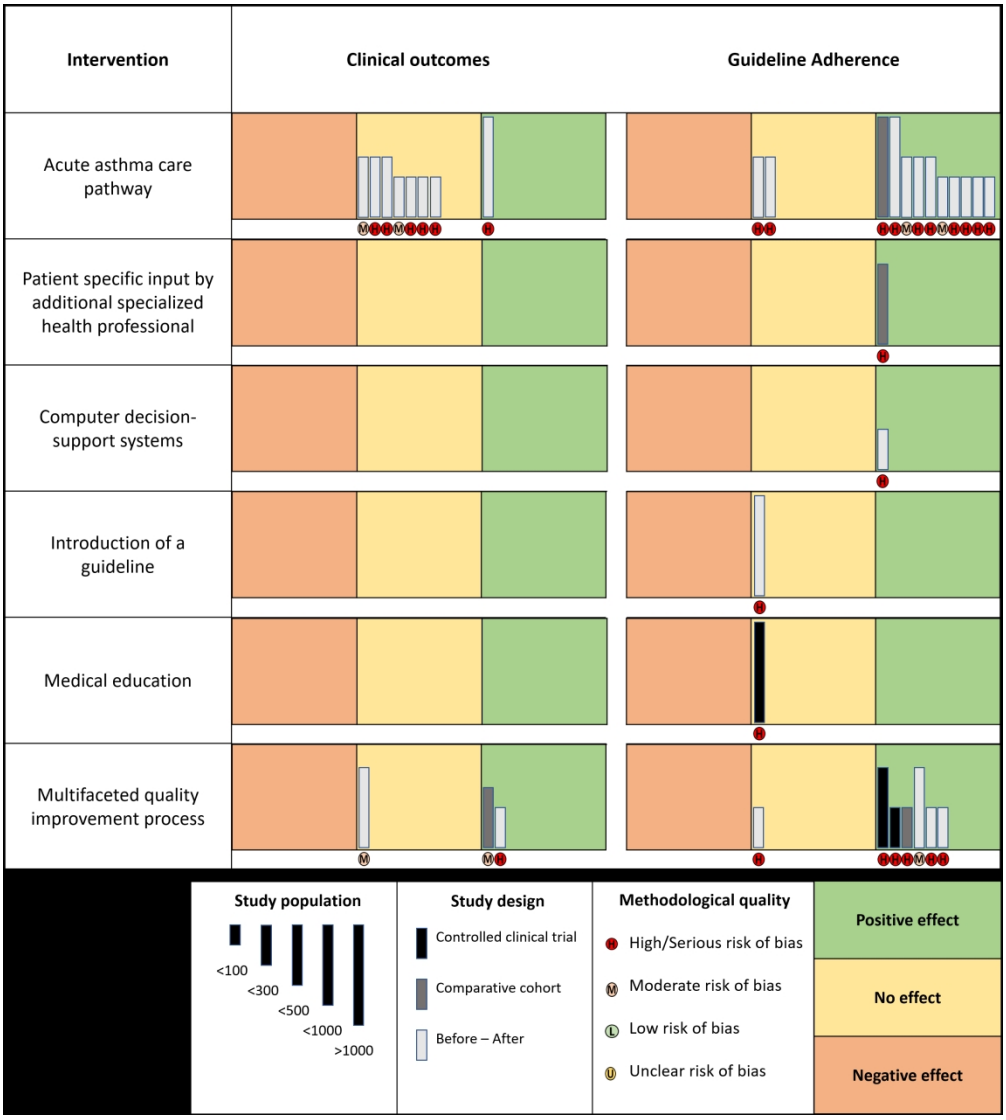
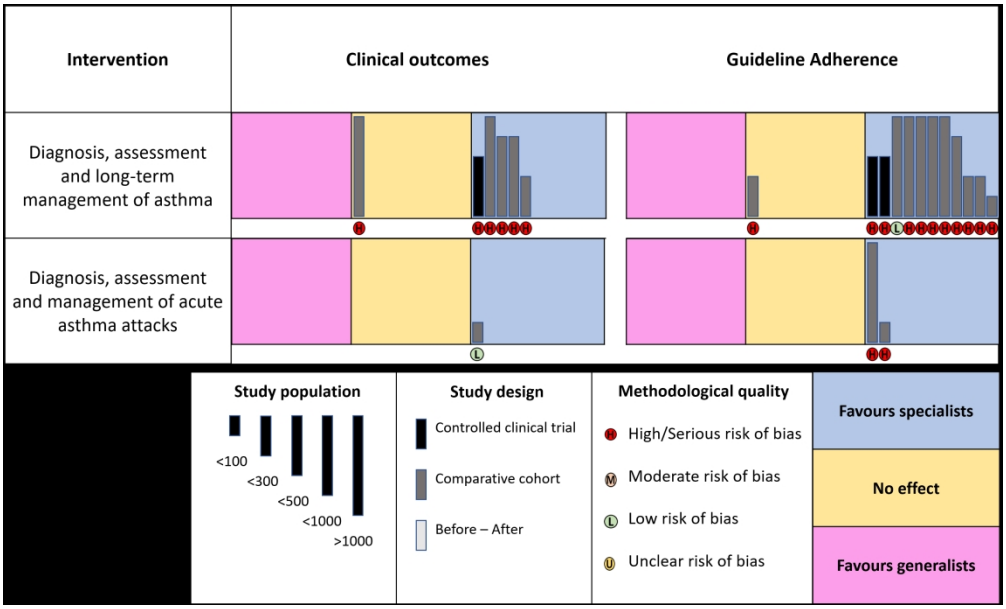


Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for asthma assessment and maintenance management.



Harvest plot summarizing the findings of studies evaluating interventions to improve guidelines adherence for acute asthma attacks assessment and management.



Harvest plot summarizing the findings of studies evaluating differences in the adherence to asthma guidelines by Specialists or Generalists.

ERS/EAACI statement on adherence to international adult asthma guidelines

Alexander G. Mathioudakis, Olympia Tsilochristou, Ian M Adcock, Andras Bikov, Leif Bjermer, Enrico Clini, Breda Flood, Felix Herth, Ildiko Horvath, Omer Kalayci, Nikolaos G. Papadopoulos, Dermot Ryan, Silvia Sanchez Garcia, Jaime Correia-de-Sousa, Thomy Tonia, Hillary Pinnock, Ioana Agache, Christer Janson.

Online Supplement

Contents:

- **Survey Questionnaires**

T2 Mild Asthma

A 22 year-old female, non-smoker, maths student attends for a consultation in October complaining about occasional chest tightness and cough (especially when playing tennis), during late spring to mid summer the last 4 years. She has never used any inhalers for her chest symptoms. Regular chest auscultation provides you with normal lung sounds.

She also mentions that during the same months she has been experiencing watery eyes and nose, nasal congestion as well as sneezing. These symptoms began early at adolescence and have been managed with as needed, over the counter antihistamines. She was diagnosed with eczema and egg allergy as a toddler with both conditions having resolved by the age of 10 years, which was the age she was last evaluated in an allergy clinic. She has a cat at home.

1st Question: What are your thoughts on your patient's health condition? (one answer applies)

1. the history of the symptoms from the lower respiratory system are typical of asthma and I can thus set the diagnosis of asthma for this patient
2. the history of the symptoms from the lower respiratory system are not typical of asthma and I need to focus on the treatment of the nasal symptoms
3. the history of the symptoms from the lower respiratory system are indicative of asthma but I need to check whether there is variable expiratory flow limitation
4. the history of the symptoms from the lower respiratory system are indicative of asthma but I need to check whether there is variable inspiratory flow limitation

2nd Question: Which of these investigations would you decide to perform/order if all were available to you? (more than one answer can apply)

- Spirometry, Bronchodilator test
- Peak flow, Bronchodilator test
- FeNO
- blood eosinophilia
- total serum IgE
- Skin prick test to common aeroallergens
- Specific serum IgE
- Chest X-Ray
- ENT examination
- Bronchoscopy
- Bronchoprovocation test
- Bacteriological exam of the sputum
- Detailed history
- Chest auscultation with fierce exhalation
- Home peak flow monitoring, including before and after playing tennis

3rd Question: Chest auscultation with fierce exhalation provides normal sounds. You had the possibility of performing spirometry and received the following outcomes: baseline spirometry resulted in FEV1/FVC ratio 0.75 and administration of 400 mcg salbutamol increased FEV1 by 10% (150 ml). What is your diagnosis and how would you manage the patient?

1. I have excluded that the patient has asthma and will discharge her by prescribing treatment for the nasal symptoms during Spring/Summer.
2. I have excluded that the patient has asthma, I will prescribe treatment for the nasal symptoms during Spring/Summer and will rebook the patient to come back in June.
3. I have not excluded that the patient has asthma, and will teach her to monitor her peak flows both when she has symptoms and when she is asymptomatic. I will rebook the patient to come back in June for lung function testing.
4. The diagnosis of asthma is certain and I will prescribe a reliever to be used during the pollen season together with the rhinitis treatment.

The patient comes back during the pollen season. She reports episodes of chest tightness and cough especially early in the morning when she is walking to work through a park and if walking back home late evening. She additionally mentions wakening up at night due to chest tightness and nasal blockage. She has been avoiding playing tennis because of these symptoms. She is receiving her antihistamine daily but no nasal spray. Regular chest auscultation provides you with normal lung sounds. Spirometry with reversibility results in 13% (220 ml) increase in FEV1 post the bronchodilator administration.

4th Question: What is the level of asthma control?

- **A.** Controlled
- **B.** Partially controlled
- **C.** Uncontrolled

5th Question: Which is the asthma severity level?

- **A.** Moderate persistent
- **B.** Severe persistent
- **C.** Mild persistent
- **D.** Intermittent
- **E.** Mild intermittent
- **F.** Moderate intermittent
- **G.** Severe intermittent

FeNO is 38 ppb. Skin prick testing with common aeroallergens elicited positive response of 9mm wheal to grass pollen mix. Blood eosinophils 210/cml

6th question: Which is the phenotype? (multiple answers can apply)

A. Type 1
B. Type 2
C. Mixed type 1 and 2
D. Allergic asthma
E. Asthma with allergic sensitization
Z. I do not know

7th Question: How would you manage the patient?

1. I will step up with her nasal treatment only
2. In addition to the nasal therapy, I will prescribe reliever treatment for her asthma to be used at pollen season.
3. In addition to the nasal therapy, I will prescribe inhaled steroids for her asthma to be used regularly according to her asthma action plan which will advise her a) what action to take if the symptoms worsen, b) how to reduce/stop the dose as symptoms resolve at the end of the pollen season and c) how to recommence treatment if/when symptoms recur. I will review her again next year, at pollen season when I know she is expected to have symptoms.
4. In addition to the nasal therapy, I will prescribe inhaled corticosteroids (ICS) to be received until symptoms disappear and will review her again next year towards the end of Spring when I know she is expected to have symptoms

8th Question: If you choose to prescribe asthma treatment, what would that be? (multiple answers can apply)

1. Low dose ICS
2. Montelukast
3. Low dose ICS/LABA
4. Moderate/high ICS dose
5. Salbutamol twice daily
6. LABA
7. Omalizumab
8. AIT

T2 Severe Asthma

A 21 year-old male, BMI=23, comes for a consultation due to coughing, shortness of breath and wheezing. He has been suffering with asthma since childhood; from 3-12 years of age he was treated with inhaled budesonide, later on with fluticasone/salmeterol 50/250 dry powder inhaler, 1 puff twice-daily, while the last 4 years with fluticasone/salmeterol 50/500 dry powder inhaler, 1 puff twice-daily. Despite this treatment, he suffers from night symptoms twice a week which prompt him to use salbutamol. Playing football or cyclying also cause asthma exacerbation especially during Spring. He complains of itchy eyes and nose, sneezing and runny nose all year round but worse during springtime. He uses loratadine on demand for his nasal and ocular symptoms.

He is a student in journalism, with no exposure to chemicals or other substances and doesn´t smoke. He lives in a house with a tree-garden in a small town, and does not keep pets.

1st question: Which of these investigations would you decide to perform/order if all were available to you? (multiple answers possible)

A) Spirometry, Bronchodilator test
B) Peak flow, Bronchodilator test
C) FeNO
D) blood eosinophilia
E) total serum IgE
F) Skin prick test to common aeroallergens
G) Specific serum IgE
H) Chest X-Ray
I) ENT examination
J) Bronchoscopy
K) Bronchoprovocation test
L) Bacteriological exam of the sputum
M) Detailed history
N) Chest auscultation
O) Serial peak flow readings
P) Check his prescribing record and discuss adherence
Q) Assess inhaler technique

Spirometry shows baseline FEV1=3.49l (76.3% of predicted), with a bronchodilator reversibility test of 28% (250ml).

2nd Question: What is the level of asthma control?

- **A.** Controlled
- **B.** Partially controlled
- **C.** Uncontrolled
- **D.** I do not know

3rd Question: Which is the asthma severity level?

- **A.** Moderate persistent
- **B.** Severe persistent
- **C.** Mild persistent
- **D.** Intermittent
- **E.** Mild intermittent
- **F.** Moderate intermittent
- **G.** Severe intermittent
- **H.** I do not know

4th Question: What would you do next (more than one answers can apply)?

- **A.** Step up treatment according to GINA recommendations
- **B.** Maintain the same treatment
- **C.** Step down because there are no activity limitations
- **D.** Investigate patient's adherence
- **E.** Evaluate the presence of comorbidities
- **F.** Evaluate inhaler technique
- **G.** Investigate the asthma phenotype

The patient has asthma symptoms when exercising outdoors during late Spring. FeNO at this time point is 113 ppb. Blood eosiniphils 500/cml and Skin prick tests are positive to grass and tree pollen, and Alternaria mold.

5th Question: Which is the phenotype? (multiple answers can apply)

- A. Type 1
- B. Type 2
- C. Mixed type 1 and 2
- D. Allergic asthma
- E. Asthma with allergic sensitization
- F. I do not know

6th Question: Is he under risk of exacerbations?

A. Yes

B. No

7th Question: Indicate the risk factors (multiple answers can apply):

A. Allergen exposure

B. Uncontrolled rhinitis

C. Blood eosinophilia

D. Impaired lung function

E. Elevated FeNO

F. Food allergy

G. Night time awakenings

H. High doses of ICS

I. Obesity

J. Aspirin sensitivity

8th question: Which would be your preferred option to control his asthma (multiple answers can apply)?

A. Tiotropium

B. Omalizumab

C. Oral corticosteroids

D. Montelukast

E. Anti-IL 5

F. Anti-IL4/13

G. Change ICS to fine particles ICS

H. Phosphodiesterase 4 (PDE4) inhibitors

I. Increase ICS dose

J. Rhinitis treatment

K. Allergen immunotherapy

9th Question: The patient returns for follow up. What tests would you choose to perform to investigate asthma control (multiple answers can apply)?

A. Asthma control test
B. Lung function with bronchodilator
C. Fe NO
D. Blood eosinophils
E. Specific IgE
F. Chest X-Ray
G. High Resolution CT scan

10th Question: Asthma control is not achieved. Which would be your preferred option as a second step? (multiple answers can apply)

A. Tiotropium
B. Omalizumab
C. Oral corticosteroids
D. Montelukast
E. Anti-IL 5
F. Anti-IL4/13
G. Change ICS to fine particles ICS
H. PD4 inhibitors
I. Increase ICS dose
J. Rhinitis treatment
K. Allergen immunotherapy
L. Referral to a Specialist/Difficult Asthma Clinic

Non T2 asthma

A 50 year-old lady attends as an emergency due to breathlessness. She reports that her dyspnea has worsened over the last two weeks despite using 2 puffs of beclomethasone dipropionate/formoterol (100/6 μg) twice daily and that she now needs to use her reliever (salbutamol) four times a day. On presentation, she talks in phrases but wheezes, her oxygen saturation is 92%, pulse rate at 118bpm, respiratory rate at 28bpm, FEV_1 72% pred., FVC 82% pred., FEV_1/FVC 0.68 while electrocardiography is unremarkable. She was diagnosed with asthma 10 years ago (PC20 for methacholine <4 mg/ml), skin prick testing to common aeroallergens was negative. Since then she has been on high doses of inhaled corticosteroids but often uses salbutamol after exercise and sometimes during the night. She has to take oral corticosteroids around 4 times a year for asthma exacerbations and was hospitalized due to asthma twice in the last 5 years (once at ICU). She is 160 cm tall, weighs 90 kg, works in a dye-factory and has been occasionally smoking the last 30 years.

1st Question: How would you manage the patient? (multiple answers can apply)

A) Hospitalize the patient immediately due to life-threatening asthma exacerbation.
B) Give 1 mg/kg intravenous prednisolone, controlled oxygen, 4-10 puffs of salbutamol and re-evaluate after 1 hour.
C) Give 50 mg intravenous prednisolone, controlled oxygen, 4-10 puffs of salbutamol and re-evaluate after 1 hour.
D) Give 1 mg/kg prednisolone by mouth, controlled oxygen, 4-10 puffs of salbutamol and re-evaluate after 1 hour.
E) Give 50 mg prednisolone by mouth, controlled oxygen, 4-10 puffs of salbutamol and re-evaluate after 1 hour.
F) Prescribe oral prednisolone 50 mg/day, send home and review response after 1 week.
G) Prescribe oral prednisolone 1 mg/kgr, send home and review response after 1 week.
H) Advise using ICS/formoterol also as a reliever (maximum 72 μg formoterol) and review response after 2 days.

2nd Question: The patient attends the follow-up consultation. Which of the following investigations would you decide to perform/order if all were available to you? (more than one answer can apply)

- Spirometry, Bronchodilator test
- Peak flow, Bronchodilator test
- FeNO
- blood eosinophilia
- total serum IgE
- Skin prick test to common aeroallergens
- Specific serum IgE
- Chest X-Ray
- ENT examination

- Bronchoscopy
- Bronchoprovocation test
- Bacteriological exam of the sputum
- Detailed history
- Chest auscultation
- Occupational exposure evaluation
- Check her prescribing record and discuss adherence
- Check inhaler technique

Spirometry results are as following: FEV1 79% pred., FVC 82% pred., FEV1/FVC 0.72, reversibility 7% (150ml). Chest auscultation normal. She still needs to use her reliever at least three times a week.

3rd Question: What is the level of asthma control?

E. Controlled
F. Partially controlled
G. Uncontrolled
H. I do not know

4th Question: Which is the asthma severity level?

I. Moderate persistent
J. Severe persistent
K. Mild persistent
L. Intermittent
M. Mild intermittent
N. Moderate intermittent
O. Severe intermittent
P. I do not know

FeNO is 6 ppb. Skin prick testing with common aeroallergens is negative. Blood eosinophils 48/cml.

5th Question: Which is the phenotype? (multiple answers can apply)

A. Type 1
B. Type 2
C. Mixed type 1 and 2
D. Allergic asthma
E. Asthma with allergic sensitization
F. Occupational asthma
G Related to her obesity
H. Asthma COPD overlap syndrome

I. I do not know

6th Question: How should the patient be managed on a long term? (multiple answers can apply)

A) There is no need to change medications.
B) Advise using ICS/formoterol as maintenance and as reliever (maximum 72 µg formoterol).
C) Add leukotriene receptor antagonist to moderate/high dose ICS/LABA bi-daily
D) Add tiotropium to moderate/high dose ICS/LABA twice daily
E) Advise taking 250 mg azithromycin 3 times a week for 3 months.
F) Change of work place
G) Anti-IL5
H) Anti-IL4/13
I) Omalizumab
J) Allergen Immunotherapy
K) Phosphodiesterase 4 (PDE4) inhibitors
L) Bronchial thermoplasty
M) Provide self-management education including an action plan

7th Question: After stepping up in the treatment, the patient still complaints of frequent need of reliever use. How would you proceed? (more than one answer can apply)

A) Re-evaluate the initial diagnosis
B) Assess for comorbidities
C) Assess adherence to treatment
D) Assess inhaler use technique
E) Prescribe regular low dose oral corticosteroids (7.5 g/day).
F) Advise smoking cessation and weight reduction.
G) Psycho-social assessment
H) Pulmonary rehabilitation

- **Search strategy**

Search 1: Systematic review of studies evaluating interventions aimed to improve adherence to asthma guidelines.

#1	Asthma[MH]
#2	Asthma[tiab]
#3	Asthma*[tiab]
#4	Anti-Asthmatic Agents[MH]
#5	#1 or #2 or #3 or #4
#6	Guideline[MH]
#7	Evidence-Based Medicine[MH]
#8	practice guidelines as topic[MH]
#9	Guideline[tiab]
#10	Guideline*[tiab]
#11	Guidance[tiab]
#12	#6 or #7 or #8 or #9 or #10 or #11
#13	Quality improvement[mh]
#14	Patient care planning[mh]
#15	Guideline adherence[mh]
#16	Outcome and Process Assessment (Health Care) [mh]
#17	Decision Support Systems, Clinical[mh]
#18	Comprehension[mh]
#19	Audit[tiab]
#20	Quality[tiab] and (improvement[tiab] or (improve*[tiab]))
#21	(guideline[tiab] or (guidance[tiab]) or (guideline*[tiab]) or (guida*[tiab])) and (adherence[tiab])
#22	Decision support[tiab]
#23	Understanding[tiab]
#24	Implement*[tiab]
#25	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#5 and #12 and #25

#27	(child[mh]or (adolescent[mh])) not (adult[mh])
#28	animals[mh] not (humans[mh])
#29	letter[publication type]
#30	editorial[publication type]
#31	review[publication type]
#32	systematic review [publication type]
#33	systematic[tiab] and (review[tiab])
#34	meta-analysis[tiab]
#35	metaanalysis[tiab]
#36	#31 NOT (#32 or #33 or #34 or #35)
#37	#26 not (#27 or #28 or #29 or #30 or #36)

Search 2: Studies assessing differences in the process and clinical outcomes in patients managed by Specialists versus Generalists.

#1	Asthma[MH]
#2	Asthma[tiab]
#3	Asthma*[tiab]
#4	Anti-Asthmatic Agents[MH]
#5	#1 or #2 or #3 or #4
#6	Referral and consultation[MH]
#7	Referral[tiab]
#8	Medical specialties [MH]
#9	specialist[tiab] or specialty[tiab]
#10	respiratory[tiab]
#11	pulmonary[tiab]
#12	allergy [tiab]
#13	allergist [tiab] or pulmonologist [tiab] or pulmonology [tiab]
#14	#9 or #10 or #11 or #12 or #13
#15	(#7 or #8) and #14
#16	#6 or #15

#17	#5 and #16
#18	(child[mh]or (adolescent[mh])) not (adult[mh])
#19	animals[mh] not (humans[mh])
#20	letter[publication type]
#21	editorial[publication type]
#22	review[publication type]
#23	systematic review [publication type]
#24	systematic[tiab] and (review[tiab])
#25	meta-analysis[tiab]
#26	metaanalysis[tiab]
#27	#22 NOT (#23 or #24 or #25 or #26)
#28	#17 not (#18 or #19 or #20 or #21 or #27)

Table e1 Results from the questionnaire survey – Mild T2 asthma (%). *P-values pertain to comparisons among the three groups, using chi-squared test.

	Allergy doctors (n=141)	**Respiratory doctors (n=542)**	**Generalists (n=78)**	P-value*
What is your diagnosis and how would you manage the patient?				
Excluded asthma discharge	1.4	0.9	1.3	
Excluded asthma rebook	2.1	1.5	6.4	0.06
Not excluded asthma	76.6	83.8	75.6	
Diagnosed asthma	19.9	13.8	16.7	
What is the level of asthma control?				
Controlled	2.9	1.5	4.0	
Partially controlled	21.3	16.9	21.3	0.29
Uncontrolled	75.7	81.6	74.7	
Which is the asthma severity level?				
Intermittent	8.1	9.0	8.0	
Mild intermittent	9.6	9.0	12.0	
Mild persistent	16.9	16.1	12.0	
Moderate intermittent	27.9	23.6	33.3	P=0.37
Moderate persistent	32.4	31.0	28.0	
Severe intermittent	0.7	5.8	1.3	
Severe persistent	4.4	5.6	5.3	
Which is the phenotype?				
Type 1	6.6	8.6	5.3	0.51
Type 2	30.2	13.6	1.3	<0.0001
Mixed type 1 and 2	1.5	5.6	10.7	0.02
Allergic asthma	79.4	61.7	56.0	<0.0001
Asthma with allergic sensitisation	33.8	34.3	46.7	0.10
Don't know	2.9	9.2	14.7	0.01
How would you manage the patient?				
Step up nasal only	0.8	0.8	1.3	
Reliever in addition	9.5	10.9	12.0	
ICS in addition + asthma action plan	882	85.6	84.0	0.91
ICS in addition + follow up	1.5	2.7	2.7	
If you choose to prescribe asthma treatment, what would that be?				
Low ICS	36.8	35.4	44.0	0.35
Montelukast	40.4	37.2	32.0	0.48
Low ICS+LABA	55.8	55.9	44.0	0.14
Moderate-High ICS	16.9	16.1	14.7	0.91
SABA twice daily	8.8	5.2	10.7	0.09
LABA	7.4	5.9	4.0	0.61
Omalizumab	2.9	1.5	4.0	0.27
AIT	48.5	6.7	2.7	<0.0001

Table e2 Results from the questionnaire survey – Severe T2 asthma (%). *P-values pertain to comparisons among the three groups, using chi-squared test.

	Allergy doctors (n=99	**Respiratory doctors (n=361)**	**Generalists (n=47)**	P-value*
What is the level of asthma control?				
Don't know	1.0	3.3	4.3	
Controlled	1.0	0.3	2.2	0.53
Partially controlled	26.3	22.4	21.2	
Uncontrolled	71.7	74.0	72.3	
Which is the asthma severity level?				
Intermittent	1.0	0.8	2.1	
Mild intermittent	1.0	3.3	4.3	
Mild persistent	4.0	6.4	6.4	
Moderate intermittent	3.0	3.6	4.3	0.66
Moderate persistent	43.4	46.0	44.7	
Severe intermittent	2.0	1.9	0	
Severe persistent	41.4	37.4	36.2	
Don't know	2.0	0.3	2.1	
What would you do next				
Step up treatment according to GINA	74.8	76.7	66.0	0.27
Maintain the same treatment	2.0	3.6	2.0	0.41
Step down because there are no activity limitations	0	0.6	2.1	0.29
Investigate patient's adherence	91.9	87.8	83.0	0.27
Evaluate the presence of comorbidities	91.9	76.4	66.0	<0.0001
Evaluate inhaler technique	98.0	90.9	89.4	0.051
Investigate the asthma phenotype	77.8	68.1	61.7	0.09
Which is the phenotype?				
Type 1	5.0	12.5	12.8	0.10
Type 2	31.3	19.4	10.6	0.007
Mixed type 1 and 2	16.2	15.5	10.6	0.65
Allergic asthma	71.7	57.1	46.8	0.007
Asthma with allergic sensitisation	36.4	31.6	29.8	0.62
Don't know	3.0	10.0	23.4	0.001
Is he under risk of exacerbations?				
Yes	99.0	94.5	91.5	
No	0	1.9	4.3	0.24
Don't know	1.0	3.6	4.3	
Indicate the risk factors				
Allergen exposure	89.9	80.1	80.8	0.08
Uncontrolled rhinitis	68.7	64.0	66.0	0.68
Blood eosinophilia	50.5	58.2	48.9	0.24
Impaired lung function	50.5	51.0	42.6	0.55
Elevated FeNO	53.5	61.5	51.1	0.18
Food allergy	11.1	11.9	10.6	0.95
Night time awakenings	63.6	68.7	60.0	0.34
High dose of ICS	36.4	41.8	40.4	0.62
Obesity	25.2	17.2	14.9	0.15
Aspirin sensitivity	14.1	13.3	10.6	0.84

Which would be your preferred option to control his asthma?				
Tiotropium	20.2	46.5	19.2	<0.0001
Omalizumab	30.3	21.0	23.4	0.15
Oral corticosteroids	21.2	16.3	10.6	0.26
Montelukast	54.6	59.8	48.9	0.28
Anti-IL 5	18.2	14.1	10.6	0.43
Anti IL4/13	5.0	3.3	0	0.28
Change ICS to ultra-fine particle ICS	25.2	34.1	27.7	0.20
Phosphodiesterase 4 inhibitors	1.0	1.7	0	0.62
Increase ICS dose	43.4	31.9	31.9	0.09
Rhinitis treatment	75.8	71.2	63.8	0.32
Allergen immunotherapy	50.5	24.1	36.2	<0.0001
. What tests would you choose to perform to investigate asthma control?				
Asthma control test	88.9	85.6	78.7	0.26
Lung function with bronchodilator test	78.8	79.8	74.5	0.70
FeNO	73.7	69.5	53.2	0.04
Blood eosinophils	37.4	44.0	29.8	0.12
Specific IgE	22.2	19.7	14.9	0.58
Chest X-ray	9.1	10.5	8.5	0.86
High resolution CT scan	6.1	5.5	4.3	0.90
Which would be your preferred option as a second step?				
Tiotropium	3.0	8.0	10.6	0.02
Omalizumab	27.3	21.0	8.5	
Oral corticosteroids	13.1	9.1	6.4	
Montelukast	5.0	5.3	4.3	
Anti-IL 5	20.2	15.8	8.5	
Anti IL4/13	2.0	2.5	0	
Change ICS to fine particle ICS	3.0	5.3	6.4	
Phosphodiesterase 4 inhibitors	0	0.6	0	
Increase ICS dose	5.0	5.0	8.5	
Rhinitis treatment	1.0	1.7	2.1	
Allergen immunotherapy	6.0	1.7	0	
Referral to Specialist/ Difficult Asthma Clinic	13.1	19.9	40.4	

Table e3 Results from the questionnaire survey – Non T2 asthma (%). *p-values pertain to comparisons among the three groups, using chi-squared test.

	Allergy doctor (n=205	**Respiratory doctors (n=338)**	**Generalists (n=134)**	P-value*
How would you manage the patient at the emergency department?				
Hospitalisation	23.4	26.6	19.4	0.24
Prednisolone 1mg/kg iv	29.3	21.6	15.7	0.01
Prednisolone 50 mg iv	16.6	23.4	9.7	0.002
Prednisolone 1 mg/kg po	16.6	9.5	13.4	0.047
Prednisolone 50mg po	17.6	24.6	26.1	0.10
Prednisolone 50 mg/day	9.8	8.9	11.9	0.60
Prednisolone 1 mg/kg/day	4.4	4.1	3.7	0.96
ICS/Formoterol as reliever	20.5	18.3	17.9	0.78
What is the level of asthma control?				
Controlled	1.3	1.1	3.3	
Partially controlled	45.7	47.6	34.4	0.16
Uncontrolled	53.0	49.4	60.0	
Don't know	0	1.9	2.3	
Which is the asthma severity level?				
Intermittent	0.7	1.1	2.2	0.88
Mild intermittent	1.3	1.9	2.2	
Mild persistent	6.6	11.5	8.9	
Moderate intermittent	2.0	2.2	3.3	
Moderate persistent	43.7	41.3	37.8	
Severe intermittent	2.6	3.7	6.7	
Severe persistent	40.0	35.3	35.6	
Don't know	3.3	3.0	3.3	
Which is the phenotype?				
Type 1	25.2	19.0	7.8	0.004
Type 2	9.9	19.0	5.6	0.002
Mixed type 1 and 2	12.6	13.0	15.6	0.79
Allergic asthma	5.3	4.1	7.8	0.38
Asthma with allergic sensitisation	0	1.9	10.0	<0.0001
Occupational asthma	29.8	34.9	23.3	0.11
Obesity related	58.3	54.3	37.8	0.006
Asthma COPD overlap	41.1	30.1	30.0	0.06
Don't know	4.6	10.8	25.6	<0.0001
How should the patient be managed on a long term?				
ICS/LABA smart	55.0	56.9	62.2	0.54
Montelukast	51.7	41.6	36.7	0.046
Tiotropium	65.6	73.2	57.8.0	0.02
Azithromycin	13.2	11.9	4.4	0.08
Occupation change	36.4	40.5	31.1	0.26
Ant IL-5	20.5	9.7	3.3	<0.0001
Anti IL-4/13	4.0	2.2	1.1	0.35
Anti IgE	11.9	4.8	3.3	0.008
AIT	4.6	1.1	4.4	0.06
Roflumilast	3.3	2.2	3.3	0.75

Bronchial thermoplasty	3.3	4.5	0	0.12
Education	72.9	72.5	71.1	0.96
After stepping up in the treatment, the patient still complaints of frequent need of reliever use. How would you proceed?				
Re-evaluation of diagnosis	75.5	72.9	80.0	0.39
Assess comorbidities	93.4	89.2	83.3	0.049
Check adherence	94.0	93.7	84.4	0.01
Check inhalation technique	94.0	95.9	88.9	0.05
Oral corticosteroids	24.5	17.1	24.4	0.12
Smoke cessation	94.0	95.2	91.1	0.37
Psycho social assessment	59.6	61.3	57.8	0.82
Pulmonary rehabilitation	36.4	50.6	52.2	0.01

Table e4 Risk of bias of the included studies (a) Randomized controlled trials; (b) Observational studies.

a.

Studies	Random sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other source of bias
Armour 2007	H	H	H	H	L	L	L
Herborg 2001	H	H	H	H	L	L	L
Manfrin 2017	H	H	H	H	L	L	L
McLean 2003	H	H	H	H	L	L	L
Pilotto 2004	H	H	H	H	L	L	L
Premaratne 1999	H	H	H	H	H	L	L
Wong 2017	H	H	H	H	H	L	L
Zeiger 2014	L	L	H	H	L	L	L
Renzi 2006	L	L	L	L	H	L	L
Eccles 2002	H	H	H	H	H	L	L
Kuilboer 2006	H	H	H	H	L	H	L
Martens 2007	H	H	H	H	L	H	L
McCowan 2001	H	H	H	H	L	L	L
Tamblyn 2015	H	H	H	H	L	L	L
Tierney 2005	H	H	H	H	L	L	L
Baker 2003	H	H	H	H	L	L	L
Feder 1995	H	H	H	H	L	H	L
Bachmann 2019	H	H	H	L	L	H	L
Baldacci 2012	H	H	H	H	L	H	L
Cleland 2007	H	H	H	H	L	L	L
Daniels 2005	H	H	H	H	L	H	L
Goeman 2009	H	H	H	H	L	L	L
Mold 2014	H	H	H	H	L	H	L
Veninga 1999	H	H	H	H	L	H	L
Blais 2008	H	H	H	H	L	H	L
Schneider 2008	H	H	H	H	L	L	L
Doherty 2006	H	H	H	H	L	H	L
Foster 2007	H	H	H	H	L	H	L
Harmsen 2010	U	H	H	H	H	L	L
Zeiger 1991	H	H	H	H	L	L	L

b.

Studies	Confounding bias	Selection bias	Classification bias	Intervention deviation bias	Attrition bias	Outcome measurement bias	Reporting bias	Overall
Coleman 2004	M	L	L	L	L	L	L	M
Dickinson 1998	S	S	L	L	L	L	M	S
Lindberg 2002	M	L	L	L	L	L	L	M
Yanchick 2000	S	L	L	L	L	L	L	S
Ruoff 2002	S	S	L	L	L	L	M	S
To 2008	S	S	L	L	L	L	L	S
Yawn 2008	S	L	L	L	L	L	M	S
Cho 2010	S	S	L	L	L	L	M	S
Kim 2015	S	L	L	L	L	L	M	S
Wright 2003	M	L	L	L	L	L	M	M
Ables 2002	S	L	L	L	S	L	L	S
Bender 2011	S	L	L	L	L	L	M	S
Cicutto 2014	S	L	L	L	L	L	M	S
Greene 2007	M	L	L	L	L	L	L	M
Jans 2000, Jans 2001	S	L	L	L	L	L	M	S
Licskai 2012	S	L	L	L	L	L	M	S
Mehring 2013	L	L	L	L	L	L	L	L
Mohammad 2019	S	S	L	L	L	L	M	S
Patel 2004	M	L	L	L	L	L	L	M
Roberts 2009	M	L	L	L	L	L	M	M
Rojanasarot 2019	M	L	L	L	L	L	M	M
Rojanasarot 2020	M	L	L	L	L	L	L	M
Andersen 2006	M	L	L	L	L	L	M	M
Abisheganaden 2001	M	L	L	L	L	L	L	M
Davies 2008	S	L	L	L	L	L	M	S
Gentile 2003	S	L	L	L	L	L	M	S
Goldberg 1998	S	L	L	L	L	L	M	S
Joe 1992	S	L	L	L	L	L	M	S
Lougheed 2009	S	L	L	L	L	L	M	S
Mackey 2007	S	L	L	L	L	L	M	S
McFadden 1995	S	S	L	L	L	L	M	C
Robinson 1996	S	L	L	L	L	L	L	S
Rowe 2008	S	L	L	L	L	L	M	S
Steurer-Stey 2005	S	S	L	L	L	L	M	S
Sukov 2000	M	L	L	L	L	L	L	M
Chew 2020	S	L	L	L	L	L	M	S

Kwok 2009	S	L	L	L	L	L	M	S
Pearson 1996	S	L	L	L	L	L	M	S
Akerman 1999	M	L	L	L	L	L	L	S
Chouaid 2004	S	L	L	L	L	L	M	S
Dalcin 2007	M	L	L	L	L	L	L	M
Doherty 2007	S	L	L	L	L	L	M	S
Edmond 1998	S	L	L	L	L	L	L	S
Pinnock 2003	S	L	L	L	L	L	M	S
Stell 1996	S	L	L	L	S	L	M	S
Abdulwadud 1999	S	L	L	L	L	L	M	S
Chou 2015	S	L	L	L	L	L	M	S
Eriskson 2005	S	L	L	L	L	L	L	S
Frieri 2002	S	L	L	L	L	L	M	S
Kanter 2002	S	L	L	L	L	L	L	S
Meng 1999	S	S	L	L	L	L	L	S
Morishima 2011	L	L	L	L	L	L	L	L
Schayck 1989	S	L	L	L	L	L	M	S
Tada 2015	S	L	L	L	L	L	L	S
Vollmer 1997	S	L	L	L	S	L	L	S
Wu 2001	S	L	L	L	L	L	L	S
Bell 1991	S	L	L	L	L	L	M	S
Pearson 1996	S	L	L	L	L	L	M	S
Pellicer 2001	L	L	L	L	L	L	L	L

Table e5 Interventions to improve guideline adherence for asthma assessment and maintenance management.

Study	Design, Size, Quality	Interventions	Clinical outcomes	Adherence outcomes
Additional patient specific input by specialised healthcare providers				
Armour 2007 Australia, 6 months follow-up	Cluster RCT, 50 pharmacies, 396 asthma patients. RoB: High (selection, performance, detection bias)	Intervention: Pharmacy Asthma Care Program (PACP), a community pharmacy-based asthma care model based on national guidelines. Pharmacists provided an ongoing cycle of assessment, management and review of pharmacy practice, in collaboration with general practitioners. Control: Usual pharmacists care.	- Higher proportion of patients improving from severe to non-severe asthma (OR: 2.68 [1.64, 4.37]). - Improvement in AQLQ (MD: -0.44 [-0.69, -0.18]), that did not reach MCID. - Lower daily dose of salbutamol (MD: -149.1mcg [-283.9, -14.14])	- Borderline improvement in BMQ scores (MD: -0.44 [-0.69, -0.18]). - Improved CQ scores (MD: 1.18 [0.73, 1.63]). - Higher proportion of participants with correct inhaler technique (48.6% more participants [39.2%, 58%]) and asthma action plan (40.4% [31.9%, 48.9%]), compared to baseline. - Higher proportion of patients adherent to preventer treatment (OR: 1.89 [1.08, 3.30]). - Higher proportion of participants using a combination of reliever and preventer medication (OR: 3.80 [1.40, 10.32]).
Coleman 2003 USA, 6 months follow-up	Comparative observational cohort, 645 asthma patients. RoB: Moderate (confounding)	Intervention: Patient specific letter (intervention packet describing specific issues identified in the management of the given patient) was sent to the patients' prescribers and pharmacists. The letter was accompanied by a laminated colour asthma education insert illustrating the national guidelines. Control: No intervention.	- Decrease in use of oral corticosteroids (suggestive of acute exacerbations) was more pronounced in the control group. (RR: 3.63 [1.73, 7.64]). - No significant impact on the number of ED visits(+), hospital visits(+) or number of hospital days(-).	- Increase in the proportion of patients receiving ICS (RR: 1.29 [0.97, 1.70], NS), LABA (RR: 3.78 [1.74, 8.22]), or at least one long-term control treatment (RR: 1.27 [0.96, 1.96]). - 46% of the participants in the intervention group, initially using high-dose SABA, were not using high-doses 6 months after the intervention. - No impact on the prescription of spacers (-) and peak flow meters (-)
Dickinson 1998 UK, 24 months (12 months before and 12 months after the intervention)	Before-After design, 1 centre, 100 participants. RoB: Serious (participants' and outcomes' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Nurse-run asthma clinic offering optimization of the inhaled therapies and inhaled devices; educational intervention to improve compliance. Control: Same patients, prior to the nurse clinic appointment		- Reduction in SABA use (MD: -1.2 [-0.5, -2.3]). - Increase in mean daily use of ICS (MD: 261 [146, 375.9]). - Improved treatment compliance (MD: 7.8% [1.34%, 14.26%]).

Herborg 2001 Denmark, 18 months (6 months baseline evaluation, 12 months post-intervention)	Cluster RCT, 31 pharmacies, 350 patients. RoB: High (selection, performance, detection bias)	Intervention: Therapeutic outcomes monitoring by a pharmacist, who identifies and resolves drug-related problems that might lead to therapeutic failure or adverse events. Control: No intervention.	- NS decrease in SABA use (25.7% decrease in the intervention vs 3.8% in the control group). - No between-group difference in the use of oral corticosteroids (-).	- Increase in the use of ICS (52.5% versus 9.1%, p=0.02) and LABA (163% increase vs 0.9% decrease, p=0.02) compared to control group. - NS decrease in the use of oral beta-2 agonists (42.2% decrease vs 1.2% increase) and theophylline (13.7% vs 7.1%), compared to the control group.
Lindberg 2002 Retrospective substudy Sweden, 2 years	Retrospective comparative cohort. 152 asthma patients. RoB: Moderate (confounding)	Intervention: Asthma nurse issuing prescriptions and/or written asthma action plans, providing information to patients and demonstrating inhalation technique. Control: No intervention.	- Lower number of ED visits in the intervention group (0.4 vs 1.1 visits)	- Higher proportion of patients who had a documented PEFR value (95% vs 71%), a PEFR diary (90% vs 19%), a spirometry performed (95% vs 60%), reversibility test (90% vs 43%), documented smoking history (90% vs 50%) and documented family history of asthma (90% vs 23%)
Lindberg 2002 Prospective substudy Sweden, 3 months	Cross-sectional patient survey. 267 asthma patients. RoB: Moderate (confounding)	Intervention: Asthma nurse practitioner (ANP) issuing prescriptions and/or written asthma action plans, providing information to patients and demonstrating inhalation technique. Control: No intervention.	- ANP group: Fewer reported at least 2 asthma attacks (6% vs 12%), night-time awakening due to asthma (26% vs 42%) or limitation in their physical activity (17% vs 28%), in the preceding week. - NS decrease in the use of SABA (57% vs 67%). - Similar EQ-5D scores.	- ANP group: Higher proportion of patients had a PEFR instrument (84% vs 50%), a written asthma action plan (66% vs 45%), received information about asthma prevention (89% vs 75%) and considered having adequate knowledge about their disease (91% vs 81%). - No difference in the proportion of patients receiving maintenance asthma therapy(+) or those who received inhalation device training(+).
Manfrin 2017 Italy, 9 months	Cluster RCT, 283 pharmacists, 1263 asthma patients RoB: High (selection, performance, detection bias)	Intervention: The Italian Medicines Use review (I-MUR). Structured face-to-face consultation with a pharmacist covering asthma symptoms, medicines used, attitudes towards medicines, adherence and identification of pharmaceutical care issues. Control: Delayed implementation of the intervention.	- Improved asthma control, measured using the Asthma Control Test (ACT, OR: 1.76 [1.33-2.33]).	- Decrease in the number of active ingredients administered to patients by 7% (p<0.01). - Improved treatment adherence by 40% at 6 months (p<0.01). - The intervention demonstrated cost-effectiveness
McLean 2003 Canada, 12 months	RCT 27 pharmacies, 631 asthma patients RoB: High (selection, performance, detection bias)	Intervention: Enhanced pharmaceutical care by an asthma trained and certified pharmacist. Control: Usual care.	- Symptom scores decreased by 50% compared to controlled. - PEFR increased by 11%. - Reduced days of work or school by 0.6 days/ month. - Reduced SABA use by 50%.	

			- 19% Improved QoL measured using the Juniper questionnaire. - 75% decrease in ED visits and in medical visits. - No difference in hospitalisations. - Decreased overall costs ($150 vs $351)	
Pilotto 2004 Australia, 9 months	Cluster RCT. 11 general practices, 170 asthma patients RoB: High (selection, performance, detection bias).	Interventions After presentation with an acute attack, trained respiratory nurses collected clinical data, reviewed patients and instructed them on inhaler technique, at presentation, two weeks and three months. General practitioners were reviewing the patients after every visit to the respiratory nurse. Control: Usual care delivered by GP.	- No difference in the mean change in quality of life (overall SGRQ and individual components) between groups. - No difference in pre- or post- bronchodilator FEV_1. - Patients in the intervention group were more likely to attend the outpatient department (8.5% vs 0%, p=0.009) but less likely to have work absences because of asthma (0% vs 7.8%, p=0.004).	
Premaratne 1999 UK, 3 years	Cluster RCT. 41 general practices, 3,621 patients surveyed at baseline and 1,613 at follow-up. RoB: High (selection, performance, detection, attrition bias)	Intervention: Intensive education of practice nurses, who in turn improved the management of patients and provided education. Control: No intervention.	- No difference in the number of patients experiencing night awakenings (3.9% from 4.0%), asthma attacks (0.6% from 0.5%), number of hospital admissions (0.91 versus 0.86%), or quality of life (+) even when correcting for confounding factors.	- Non-significant increase in the proportion of patients receiving any maintenance treatment and specifically those receiving ICS in the intervention, compared to the control group. - Non-significant increase in the rate of patients possessing a peak flow meter and those who have received an asthma action plan.
Wong 2017 Malaysia, 1 year.	Cluster RCT. 4 government health clinics, 157 asthma patients. RoB: High (selection, performance, detection, attrition bias)	Intervention: Introduction of a pharmacy management service to monitor asthma control (ACT), inhaler technique and medication adherence, using the Malaysian Medication Adherence Scale. Control: No intervention.	- Significantly higher proportion of patients achieving well-controlled asthma (90% vs 28.6%). - Significant improvement in asthma control test scores (p<0.001). - Reduction in the use of reliever medications (MD: -4.34 [-4.47, -2.74]).	- Significantly higher proportion of patients with correct inhaler's technique (change from baseline: 80.3% versus 15.6%). - Significantly higher medication adherence (92.5% versus 45.5%).
Yanchick 2000 USA, 2 years (1 year before, 1 year after)	Before-After study Primary care department of a hospital 300 asthma patients.	Intervention: Pharmacy department established a drug therapy monitoring clinic responsible for initiating and monitoring treatment plans,	- 88% decrease in ED visits and 92% decrease in hospital admissions for asthma exacerbations.	- Significant increase in the use of spacers (98% from 25%), peak-flow meters (88% from 12%) and asthma action plans (98% from 0%).

	RoB: Serious (confounding)	implementing clinical guidelines, providing educational programs, collecting and analysing outcome data. Control: Before	- Decreased SABA use (0.25 from 2.6 canisters of albuterol per month per person) - Increase in the proportion of controlled patients (95% from 11%).	- Increased proportion of patients received training on triggers avoidance (82% from 12%).
Zeiger 2014 USA, 1 year post-intervention ** both primary and secondary care.*	RCT 1,999 asthma patients RoB: High (performance & detection bias)	Patients using ≥7 SABA canisters in a year identified through pharmacy records. Intervention: Individualized recommendations were sent to patients and physicians. Control: Standard care, no intervention.	- Decreased SABA use (less patients used ≥7 canisters during follow-up, 50.7% vs 57.1%, p=0.007). - Unchanged asthma exacerbations, number of oral steroid courses, ED visits or hospitalizations.	- More visits to allergists (30.9% vs 16.8%) - Higher percentage of patients achieved ≥0.5 controller medication ratio (45.6% vs 37.4%, p<0.001)
Asthma care pathway				
Renzi 2006 Canada, 6 months	Cluster RCT, 104 primary care physicians, RoB: High (Attrition bias)	Intervention: Self-inking stamp checklist summarizing Canadian Clinical Practice Guidelines criteria for assessing asthmatic patients' control and therapy. Co-interventions: Group A: (i) CME event + (ii) encouragement to use the stamp + (iii) request to recruit 6 patients, where the stamp will be used. Group B: i + ii, Group C: I, Control: Guidelines were posted to the physicians (Group D).	- Decrease in patients with ER visits (7.8% vs 13.5%, P=0.009) and a trend over decreased hospitalizations (2.2% vs 4%, p=0.09)	
Ruoff 2002 USA, 6 months	Before-After study Private family practice group. 122 asthma patients. RoB: Serious (participants' and outcomes' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Flow sheets highlighting 14 clinical quality indicators were introduced in patient records, to be found by clinicians during next patient visit. Control: Before		- Higher proportion of patients receiving flow meter education (63.13% from 7.07%), inhaler technique education (78.95% from 7.07%), allergy skin testing (83.33% from 34.34%), yearly PFT (84.21% from 8.08%), vaccine prophylaxis (31.25% from 9.18%). - Increased documentation about nocturnal awakenings (94.74% from 4.04%), restricted physical activities (84.12% from 2.02%), hospitalizations (73.68% from 2.02%), ED visits (73.68% from 1.01%), frequency and timing of attacks (84.21% from 3.03%), days of

				school/work missed (73.68% from 1.01%), infections (83.33% from 21.21%). - Lower proportion of patients receiving smoking cessation advice (28.57% from 66.67%)
To 2008 Canada, 12 months	Before-After study 8 primary care practices, 1408 asthma patients. RoB: Serious (participants' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Primary Care Asthma Pilot Project involving an asthma care map, treatment flow chart, programme standards, a written asthma plan and, core elements of asthma education. Followed a participatory approach. Control: Before	- Reduction in self-reported asthma exacerbations (OR: 0.35 [0.28, 0.43], ED visits due to asthma (OR 0.47 [0.32, 0.62]), school absenteeism (OR: 0.37 [0.25, 0.54]), productivity loss (OR 0.49 [0.34, 0.71]), uncontrolled asthma symptoms, daytime (OR:0.34 [0.27, 0.42]) and night-time (OR: 0.29 [0.23, 0.37]).	- Increase in the proportion of patients receiving an asthma action plan (OR: 2.41 [1.88, 3.07]), using a PEFR (OR:3.39 [2.64, 4.35]) and those who had spirometry (19.82 [12.18, 32.27]). - Decreased number of participants had asthma education in the preceding (OR: 0.43 [0.35, 0.53])
Yawn 2008 US, 9 months	Before-After study 24 primary care practices. 194 physicians and 17 other clinicians, 1,691 people with asthma. RoB: Serious (outcomes' selection, confounding).	Intervention: The asthma APGAR tools including (i) a patient survey to collect information found on control scores, with the addition of patient reported information on asthma triggers, adherence and perceptions; and (ii) an asthma management algorithm. Control: Before		- Increase in the documentation of activity modification due to asthma (100% from 29-58%), daytime (81% from 62%) and night time (65% from 25%) symptom frequency, triggers (79% from 30%), treatment adherence (94% from 32%) and response (85% from 48%). - Increased prescription of anti-inflammatory medications (73% from 24%) - Increase in inhalers' technique testing (54% from 22%) and asthma education (54% from 8%) - Increase in the proportion of patients who had non-urgent asthma visit (21% from 4%)
Computer Decision Support Systems				
Cho 2010 Korea, 3 months ** Secondary care*	Before-after study, 377 physicians, 2,042 asthma patients, RoB: Serious (participants' selection, outcomes' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Easy asthma management programme; provides decision-making support for assessing asthma severity, choosing appropriate treatments and proper monitoring during follow-up. Training was offered on the use of the software and general training material. Control: Before.	- Significant improvement in diurnal and nocturnal symptom scores of asthma patients enrolled in the EAM pilot. - Significant improvement of the self-assessed asthma symptom improvement	- Significantly decreased prescription for oral beta-2 agonists (p=0.02), oral methylxanthines (p<0.001), and systemic corticosteroids (p<0.001) for maintenance treatment. - Significant increase in the prescription of inhaled corticosteroids combined with beta-2 agonsits.

Eccles 2002 UK, 24 months (intervention administration: at 12 months)	Cluster RCT, 60 practices, 2363 asthma patients RoB: High (selection, performance, detection, attrition bias)	Intervention: Computer decision support system prompting clinicians to follow guidelines, offering suggestions for management (including prescribing). Training workshop and materials. Control: Usual care	- No effect on SF-36, EQ-5D, the Newcastle asthma symptoms questionnaire, or the asthma quality of life questionnaire.	- No differences in the proportion of patients who the following assessments: lung function (OR: 0.94 [0.67, 1.33]), medication compliance (OR: 0.82 [0.58, 1.15]), asthma education and/or action plan (OR: 0.84 [0.4, 1.74]), smoking status (OR: 0.97 [0.65, 1.45]), or those who referred for smoking cessation advice (OR: 0.75 [0.45, 1.26]). - No difference in the proportion of patients who were prescribed on SABA (OR: 1.04 [0.83, 1.31]), ICS (OR: 0.95 [0.78, 1.16]), LABA (OR: 0.84 [0.59, 1.20]), oral steroids (OR: 1.0 [0.82, 1.22]) or oral bronchodilators (OR: 1.38 [0.56, 3.39]).
Kuilboer 2006 Netherlands, 10 months (5 months baseline, 5 intervention)	Cluster RCT, 32 general practices, 9798 asthmatic patients. Rob: High (selection, performance, detection, reporting bias)	Intervention: AsthmaCritic, a computer decision support system offering suggestions/ feedback regarding physicians' decisions. Control: No intervention.		- Modestly increased number of planned asthma visits, peak-flow measurements, which however did not reach statistical significance in people of a higher age. - No difference in FEV_1 measurements among adult patients. - Decreased prescription of cromoglycate in younger ages.
Martens 2007 Netherlands	Cluster RCT, 53 GPs (14 practices), 89,358 patients with various presentations. Asthma numbers were not specified. RoB: High (selection, performance, detection, reporting bias)	Intervention: Computer reminder system containing reminders regarding alternative drug types, doses, administration routes, indications, duration of prescribing, non-pharmacological options. Control: No asthma intervention.		- Increased prescription of maintenance treatment for mildly persistent asthma (44% versus 27%). Increased use of ICS among all asthma patients (33% vs 25%). No difference in the prescription of SABA or SAMA.
McCowan 2001 UK, 6 months	Cluster RCT, 19 practices, 477 patients RoB: High (selection, performance, detection bias)	Intervention: Computer decision support system prompting clinicians to offer appropriate care (including prescribing). Control: Usual care.	- Decrease in patient-initiated consultations (OR: 0.59 [0.37, 0.95]); no impact on the number of practice initiated reviews (OR: 0.69 [0.21, 2.21]), hospital admissions (OR: 0 [0, 3.44]), ED presentations (OR:0 [0, 9.16]) or outpatient visits (OR: 0.64 [0.09, 3.38]). - Decrease in the number of exacerbations (OR: 0.43 [0.21, 0.85]) and the use of emergency nebulisations (OR: 0.13 [0.01,	- No impact on the proportion receiving a flow meter (OR: 1.52 [0.58, 4.01]), or a self-management plan (OR: 1.32 [0.42, 4.16]).

			0.91]), without any impact on the use of oral corticosteroid (OR: 0.42 [0.14, 1.29])	
Tamblyn 2015 Canada, up to 33 months	Cluster RCT, 81 GPs, 4,447 asthma patients. RoB: High (selection, performance, detection bias)	Interventions: ADS system using Canadian consensus guidelines to address problems in asthma management: recognition of poor asthma control; underutilization of prophylactic therapy lack of asthma action plan, insufficient patient education and support for self-monitoring. Training offered. Control: Standard care, which included electronic patient records.	- Non-significant decrease in the rate of out-of-control asthma rate (46.2 vs 54.7 per 100 patients per year, -8.7 [-24.7,7.3]. - Significant decrease among those with out-of-control asthma at presentation (-28.4 [-55.6,-1.2])	- Significant increase in the ratio of doses of inhaled corticosteroid use to fast-acting beta-2 agonists in the intervention group (difference 0.27 [0.02-0.51]).
Tierney 2005 USA, 3 years (2 years baseline, 1 intervention)	2x2 factorial RCT, 246 physicians (internists) & 20 outpatient pharmacists, 706 patients. RoB: High (selection, performance, detection bias)	Intervention: Computer generated encounter form listing medications and care suggestions. It also included a list of all medications for which the patient was eligible. These were given to intervention clinicians & pharmacists. Control: no intervention	- No impact on quality of life measured with SF-36, or symptoms, measured with AQLQ. - No impact on the number of ED visits or hospitalisations for any cause, or for airway diseases exacerbations.	- No differences in adherence to care suggestions. • Authors commented this may have been an underpowered study.
Guideline introduction (local or national)				
Baker 2003 UK, 2 years (1 year baseline, 1 year post-intervention)	Cluster RCT, 81 general practices, 2,679 asthma patients RoB: High (selection, performance, detection bias)	Intervention: Guidelines dissemination, prioritized review criteria, (i) with or (ii) without feedback. Control: Guidelines dissemination alone.	- Small increase in asthma symptom scores compared to control, that did not exceed MCID (p=0.02)	- No difference in the documentation of diagnostic criteria used (+), the use of PFR diurnal variation or variability for confirming equivocal diagnosis (-). - No difference in LABA prescription rate (-), evaluation of adherence (-), evaluation of SABA requirements (-), smoking cessation advice (+). - No difference in patients satisfaction with clinical care (-) or the information received (-).

Feder 1995 UK, 1 year.	Cluster RCT, 24 general practices, 240 asthma patients RoB: High (selection, performance, detection, reporting bias)	Intervention: Introduction of local guidelines with local educational interventions and a stamp checklist. Control: No intervention.		- Increase in the proportion of patients who had their inhaler technique checked (RD: 12.9 [1.9, 23.9]). - No impact on peak flow documentation (RD 0.7 [-15.2, 16.2]), symptoms review [RD: 1.0 [-13.8, 15.9]), evaluation of occupation (RD: 12.6 [-4.9, 30.2]), smoking evaluation RD:5.6 [-17.2, 28.3]). **Subgroup where the stamp was used:** Significant improvement in all parameters: peak flow evaluation (OD: 27.3 [8.1, 92.1]), inhaler technique (OR: 41.6 [17.1, 100.9]), Symptoms review (OR: 44.9 [6.1, 333.5]), Occupation (OR: 15.3 [6.9, 34.0]), smoking evaluation (OR: 66.7 [9.0, 465.8])
Kim 2015 Korea, 8 years.	Retrospective health insurance claims database review, Before-After design. 235,755 asthma patients. RoB: Serious (outcomes' selection, confounding).	Intervention: Introduction of the "Korean Asthma Management Guideline 2007". Control: Before.		- Significant increase in the ICS prescription rate (16.4% vs 13.3%, p<0.001). However, the overall trend of ICS prescription rate, estimated using the trend before guideline dissemination, did not change. Subgroup analyses according to the health setting revealed that the dissemination of the guideline led to modest increase in ICS use in secondary (OR: 1.15 [1.02, 1.30]) and general hospitals (OR: 1.10 [1.04, 1.16]), but not in primary care (OR: 0.98 [0.94, 1.02]), here most patients were reviewed
Wright 2003 UK, up to 5 years baseline (retrospective), and up to 10 months post-intervention	Prospective, comparative cohort. 180 general practices, 1453 asthma patients. RoB: Moderate (outcomes' selection, confounding)	Intervention: National, evidence-based guideline implementation including developmental interventions (to obtain commitment and adapt to a local summarized guideline and agree on implementations strategy), dissemination (education meetings and educational outreach visits) and reinforcement. Control: Passive dissemination of the guideline.		- Non-significant decrease in the proportion of clinicians reporting smoking status (MD:-7 [-14,0]) - Non-significant increase in the proportion of patients receiving inhaler technique training (MD:2 [-2, 6]) - Significant increase in the prescriptions of bronchodilators and ICS, perhaps due to seasonal effects. - Higher proportion of clinicians in the control group had seen the guideline (75% vs 25%).
Medical education				
Ables 2002	Before-after study. 1 Family Care Center,	Intervention: Three compulsory lectures on (i) electronic patient	- Decrease in the number of ED visits (from 3 to 0) and hospitalizations (from 2 to 0),	- Significant increase in the documentation of asthma severity classification from 25 to 51% (p <0.001).

US, 1.5 years (baseline, intervention, post-intervention, 6 months each).	301 asthma patients and/or AR. RoB: Serious (confounding, missing data).	records, (ii) asthma severity and classification and (iii) inhaler's technique; additional instructions for attending physicians; pocket cards; reminders in patient notes. Control: Before.	although not all events may have been successfully tracked.	
Bachmann 2019 US, 3 years (baseline, intervention, post-intervention, 1 year each).	Cluster RCT. 49 general practices, 5070 asthma patients. RoB: Serious (selection, performance, reporting bias	Intervention: Training in the use of Practical Approach to Care Kit (PACK) guide, a decision support tool. Initial and maintenance training including short interactive group sessions (90'), weekly or fortnightly. Control: PACK guide without trianing		- Borderline increased likelihood of starting or changing treatments (19% vs 15.1%, p = 0.012) and of having a spirometry requested (11% vs 8.1%, p = 0.012). - Increased asthma scores (reflecting the treatment step patients are offered and whether they had spirometry). However, significance was lost in adjusted analyses. - No improvement in the assessment of comorbidities and smoking cessation practices.
Baldacci 2012 Italy, 1 year.	Cluster RCT. 107 GPs, 1820 asthma patients. RoB: High (selection, performance, detection, reporting bias).	Intervention: Single course on ARIA and GINA guidelines, patient and caregiver education. Immunotherapy, prescriptions appropriateness and pharmacoeconomy. Control: No intervention.		- No significant between group difference in the adherence to GINA guidelines.
Bender 2011 US, 3 years (2 intervention, 1 pot-intervention).	Before-after study. 57 primary care practices, 15,508 asthma patients RoB: Serious (outcomes' selection, confounding	Intervention: 3 half-day in-practice coaching visits focusing on asthma diagnosis, management, guidelines, pathogenesis, effective communication, case studies, case discussion. Practices also received spirometers and patient toolkits. Control: Before		- Higher proportion of patients received inhaled corticosteroids (50% from 25%). - Significant increase in the proportion of patients with an asthma action plan (20% from 0%). - Significant increase in the proportion of patients who had spirometry at least once (40% from 0%).
Bender 2015 US, 2 years.	Before-after study. 13 primary care clinics, 2,392 asthma patients. RoB: Serious (outcomes' selection, confounding).	Intervention: A full-day training followed by 2 in clinic follow-up visits, spirometry demonstration and practice every year. Introduction of care and action plan templates in the electronic patient records. Online toolkit with access to manuals, patient materials, videos on spirometry and		- Significant increase in the documentation of spirometry from 6.7% to 42.5%, guideline-based severity assessment from 12.8% to 29.4%, asthma action plan administration from 1.8% to 7.6%, and prescription of ICS from 33.1% to 41.6%. However, more than half of asthma patients did not receive this 4 elements.

		patient communication, FAQs and links to other web resources. Control: Before.		
Cicutto 2014 US, 18 months post-intervention	Before-after study. 2 hospital outpatient centres and 1 community health centre, 767 asthma patients. RoB: Serious (outcomes' selection, confounding).	Interventions: Multidisciplinary, interactive workshops, asthma champion workshop for local clinic site leaders, coaching visits in clinics, clinician support tools, patient education materials and teaching aids, resource websites, provider practice feedback reports. Control: Before		- Significant improvements in all domains assessed: at least one spirometry documented (14% from 3%), documentation of asthma control (any control indicator 67% from 59%; complete assessment: 20% from 1%), reliever inhaler prescription (94% from 55%), controller medicine prescription (71% from 39%), inhaler technique demonstration (18% from 1%), asthma action plan (29% from 2%), follow-up visit arrangement (37% from 20%). - Prespecified targets were only met for the prescription of reliever medication and inhaler technique demonstration.
Cleland 2007 UK, 6 months	Cluster RCT. 13 general practices, 629 asthma patients. RoB: High (selection, performance, detection bias)	Intervention: 3-hour interactive seminar using active learning techniques. Included brief lectures, effective communication training, case studies, role play and patient resources. Control: No intervention.	- Statistically significant improvement in the mini-AQLQ, that did not exceed the MCID. - No difference in the ACQ, SABA use or number of oral steroid courses.	
Daniels 2005 USA, unclear duration.	Cluster RCT. 16 community health centres, 400 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Two half-day training sessions using principles of active adult learning focusing on the definition, classification, treatment, and prevention of asthma. Tools to support practice-level change (templates and flowcharts). Finally, resources, including asthma kits with peak flow meters, spacers and educational material. Control: No intervention.		- Statistically significant increase in the use of peak flow in the clinic (+39% vs +0.7%, p=0.008) and in the documentation of interval symptom history (+11% bs +0.04%, p=0.006), compared to the control group. - Trend over increased documentation of the family smoking history (+18% vs +10%, NS), discussion of environmental factors (+10% vs +0.7%, NS), reinforcement of maintenance and rescue plans (+19 vs +3%, NS), prescription of inhaled anti-inflammatory (+19% vs +9%, NS), and scheduling follow-up visit (+28% vs +11%)
Goeman 2009 Australia, 4 months	Cluster RCT. 42 GPs, 107 asthma patients.	Intervention: 2-hour session, participation in videorecorded simulated patient consultation, 1-hour academic detailing visit at GPs usual	- No significant changes in patients' outcomes (asthma symptom control, quality of life, lung function, treatment adherence, or asthma knowledge.	- Non-significant increase in asthma plan ownership (29% vs 15%).

	RoB: High (selection, performance, detection bias)	practice location for individually tailored training/ Control: Information packs, and a simulated patient consultation		
Greene 2007 USA, 2 years (1 year baseline data, 1 year post-intervention) * Secondary care	Before-after study. 118 residents, 441 asthma patients. RoB: Moderate (confounding).	Intervention: 12 one-hour didactic sessions using chronic care model to teach system-based practice and practice-based learning and improvement. Intensive chart reviews and quality improvement projects to promote understanding of the evidence and sharpen skills in analysing and solving problems. Control: No intervention.	- Significant decrease in the ED visits for asthma (-43.8% vs -2.9%) and for any cause (-28.7% vs +2.0%). - Significant cost benefit (36% decrease in costs in the intervention arm).	
Mold 2014 USA, 6 months **Local learning collaboratives evaluated as educational intervention here*	Cluster RCT. 43 general practices, 1,016 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Monthly-one hour sessions for practice facilitation (PF) with or without local learning collaboratives (LLC), in addition to control intervention. Control: Performance feedback, academic detailing, asthma guidelines and a toolkit with the ACT, asthma APGAR and asthma action plans.		- PF+LLC, LLC, PF and control, led to statistically significant improvement in 5, 4, 3 and 2 out of six guideline implementation indicators compared to baseline. - In multivariate modelling, PF was associated with a significantly improved assessment of asthma severity (OR: 2.5 [1.7-3.8]) and assessment of the level of asthma control (OR: 2.3 [1.5-3.5]), while LLC was not superior to control for any indicator.
Veninga 1999 Netherlands, Norway, Sweden, Slovakia, 12 months.	Cluster RCT. 665 GPs. RoB: High (selection, performance, detection, reporting bias)	Intervention: Two educational meetings. Self-learning based on individual auditing and feedback of performance for small peer groups. Control: Educational intervention about a different disease (not asthma).		- No significant changes in the proportion of patients receiving ICS, continuous bronchodilator therapy, receiving adequate ICS dose, or the proportion of patients receiving oral corticosteroids
Quality improvement process				
Blais 2008 Canada, 33 months (12 baseline, 9 intervention, 12	2 RCTs, one with 71 physicians and one with 57 pharmacists. RoB: High (selection, performance, detection, reporting bias)	Intervention: Audit and 3 consecutive letters providing feedback on participants practice (compliance with five appropriate-use criteria). Control: No intervention		- No differences were observed, as the rates of timely SABA renewal, LABA and LABA/ICS prescriptions were similar between groups.

post-intervention)				
Jans 2000, Jans 2001 Netherlands, 1 year	Before-after study. 14 general practices, 370 asthma patients. RoB: Serious (outcomes' selection, confounding).	Intervention: Identification of barriers, training on lung function, pharmacotherapy, inhalation techniques, ways to improve appointment system and referrals. Frank discussion of controversial aspects of the guidelines. Practice feedback and peer review. Control: no intervention & before.	- Statistically but not clinically significant improvement in morning PEFR (between group difference: 2.3 [0.3-4.2]) and deterioration in emotional reactions score (difference: -3.4 (-6.7, -0.1). No changes in other indicators.	- Significant increase in the percentage of patients with two or more consultations per year to monitor symptoms (82% vs ~20%). - Significant increase in the proportion of patients with at least one PEFR measurement (84% vs ~ 20%). - Significant increase in monitoring of medication compliance (60% vs 50%) and inhalation technique (42% vs 21%). - More persons quitted smoking or were advise to do so in the intervention group (84% vs 59%). - No significant between-group difference in the prescription of anti-inflammatory agents, influenza vaccination, or FEV_1 measurement.
Licskai 2012 Canada, 2 years.	Before-after study. 33 GPs, 519 asthma patients. RoB: Serious (outcomes' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Patient, practice, and health system level targeting. Problem identification, education, identification of barriers and select, tailor, implement interventions for change. Control: Before.	- Significant decrease in patients with at least one or more symptoms beyond acceptable limits (36% from 67%). This was maintained on long-term follow-up (22 months). - Sigificant decrease in urgent healthcare utilization visits (1.45±2.91 visits/year, from 2.94±4.36).	- Despite of a good baseline implementation of the six guideline-based care objectives, there was an increase in the proportion of patients prescribed controller therapy (95% versus 86%) and after the intervention, 98% of those requiring controller therapy, were prescribed.
Mehring 2013 Germany, 5 years	Longitudinal evaluation Primary care in Bavaria, 109,042 asthma patients. RoB: Low	Intervention: German Disease Management Programs include quality improvement measures with half-yearly feedback reports and benchmarking, introduction of standards, medical education, introduction of reminder systems and financial incentives to patients. Control: Before	- Significant decrease in hospital admissions (0.7% from 2.8%). - Significant increase in the proportion of patients with less than weekly or no symptoms at all (69.8% from 59.3%).	- Steady increase in the number of patients included in the DMP program (109k pts in 2010, from 21k in 2006). - Decrease in the prescription of oral corticosteroids (5.9% from 15.7%). Small decrease in SABA use, with parallel increase in the use of LABA. - Significant increase in the proportion of patients with an asthma action plan (69.3% from 40.3%) and those receiving self-management education (23.4% from 4.4%).
Mohammad 2019 Syria,	Before-after study	Intervention: Audit form to assess initial prescription of ICS/LABA by residents. Filled forms were reviewed		- Increase in the proportion of patients treated in line with guidelines (80% from 15.6%, p=0.002)

* Secondary care	1 Hospital (internal medicine department), 90 patients RoB: Serious (participants' and outcomes' selection, confounding).	by a trainer respiratory physician for compliance. In case of discrepancies, on-site training was provided. Control: Before.		- Increase in the proportion of patients receiving education for treatment avoidance (95.6% from 64.4%, p = 0.004). - All audited patients received inhaler technique training and an asthma self-management plan both before and after the intervention.
Mold 2014 USA, 6 months **Practice facilitation is evaluated as a quality improvement process here*	Cluster RCT. 43 general practices, 1,016 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Monthly-one hour sessions for practice facilitation (PF) with or without local learning collaboratives (LLC), in addition to control intervention. Control: Performance feedback, academic detailing, asthma guidelines and a toolkit with the ACT, asthma APGAR and asthma action plans.		- PF+LLC, LLC, PF and control, led to statistically significant improvement in 5, 4, 3 and 2 out of six guideline implementation indicators compared to baseline. - In multivariate modelling, PF was associated with a significantly improved assessment of asthma severity (OR: 2.5 [1.7-3.8]) and assessment of the level of asthma control (OR: 2.3 [1.5-3.5]), while LLC was not superior to control for any indicator.
Patel 2004 US, 1.5 years (6 months baseline and 1 year post-intervention)	Before-after study. 16 general practices, 6,486 asthma patients. RoB: Moderate (confounding).	Intervention: Identification of barriers and obstacles, education and implementation of best practices identified through literature review and participation in a citywide asthma advocacy organisation. Control: Before	- Decreased ED visits (88/1000 patients, from 148/1000) - Decreased hospital admissions related to asthma (37/1000 patients from 81/1000).	- Significantly improved documentation for asthma diagnosis (98.6% from 83.3%) and for patient education (26.1%, from 15.7%). - No improvement in documentation of peak flow ownership/use, smoking cessation advice, or influenza vaccination
Roberts 2009 US, 2 years	Before-after study. 1 Academic pulmonary division, 650 asthma patients. RoB: Moderate (outcomes' selection and confounding).	Intervention: Education, selection of performance indicators, auditing, quarterly confidential clinician performance feedback scorecards. Control: Before		- Significantly improved adherence to asthma management guidelines (98% from 76-92%). - Significantly increased proportion of patients prescribed ICS (96% from 83.5%).
Rojanasarot 2019 USA, 1.5 years (1 year intervention, 6	Before-after study. 65 community health centres, 4,393 asthmatic patients. RoB: Moderate	Intervention: Enhancing care of patients with asthma quality improvement process. The process included improvement activities using the Plan-Do-Study-Act (PDSA) cycle		- Significantly increased documentation of the following domains: Asthma severity (RR 1.44 [1.33-1.56]), asthma control test (3.85 [3.41-4.36]), pulmonary function testing (1.95 [1.62-2.34]), asthma education (RR 2.21 [1.99-2.45]), asthma action plan (RR 2.32 [2.03-2.65]), controller

months post intervention)	(outcomes' selection and confounding).	and learning collaboratives with other centres. Control: Before.		medication prescription (RR 1.97 [1.516-2.57]). These changes persisted six months after the intervention.
Rojanasarot 2020 USA, 3 years (1 year baseline, 1 year intervention, 5 months post-intervention)	Interrupted time series. 15 health centres in 4 States, 1,828 asthma patients. RoB: Moderate (confounding)	Intervention: Quality improvement based on Plan-Do-Study-Act cycles to carry out changes that led to asthma guidelines adoption. Control: Before	- Significant decrease in the average number of ER visits and hospitalizations due to asthma from 2.22 to 1.38 and from 1.97 to 1.04 per 100 patients, per month, respectively. Post intervention, the respective rates were 1.02 and 1.09 per 100 patients per month.	
Schneider 2008 Germany, 1 year	Cluster RCT. 96 GPs, 256 asthma patients. RoB: High (selection, performance, detection bias)	Intervention: Quality improvement circles with auditing and benchmarking, where GPs receive individual feedback and the names of the best performing GPs, who would then explain how best practice was achieved. Control: Traditional quality improvement, without benchmarking.	- Non-significant trend towards decreased frequency of unscheduled ED visits.	- Non-significant trend towards improved guideline adherence in drug treatment. - Significant increase in the delivery of individual emergency plans in both arms, however the overall use remained low, at 10-15% of patients. - No change in asthma education, peak flow meter at home and use of asthma diary. - No difference between the interventions.
Participation in a clinical trial				
Andersen 2006 Denmark, 3 years (1 year baseline, 1 intervention, 1 post-intervention)	Observational cohort study. 175 general practices, 65,013 asthma patients. RoB: Moderate (outcomes' selection, confounding)	Intervention: Participation in an RCT evaluating the asthma management (comparing to different doses of Symbircort). Control: No intervention.		- Significantly improved prescription patterns were observed in both groups. However, no difference between groups was observed in the use of either non-fixed or fixed ICS and inhaled beta-2 agonist, or on the use of the trial sponsor's drug.

*AQLQ: Asthma-related quality of life questionnaire, BMQ: Brief Medication Questionnaire, CQ: Consumer asthma knowledge questionnaire, ED: Emergency Department, MCID: Minimal clinically important difference.

Table e6 Interventions to improve guideline adherence for acute asthma attacks assessment and management.

Study	Design, Size, Quality	Interventions	Clinical outcomes	Adherence outcomes
Acute asthma care protocol/pathway				
Abisheganaden 2001 Singapore, 9 months	Before-after study. Community-based teaching hospital, 183 asthma patients RoB: Moderate (confounding)	Intervention: Introduction of an asthma care pathway. Control: Before.	- No significant change in length of stay. - No significant change in asthma relapse after discharge.	- No change in the use of PEFR monitoring, or the use of systemic corticosteroids. - Decrease in the use of antibiotics (30.4% from 62.7%) and request of sputum tests (18.6% from 34.3%). - Increase in the proportion of patients who had their salbutamol (73.7% from 49.3%) and oxygen (73.8% from 25.8%) reviewed.
Davies 2008 Canada, 1 year (3 months baseline, 6 months intervention, 3 months post-intervention).	Before-after study. Community hospital, 128 asthma patients. RoB: Serious (outcomes' selection and confounding)	Intervention: Clinical pathway introduction, medical education including 2x2-hour core sessions, pre-learning package and supportive information. Local champions appointed as mentors and advocates. Control: Before		- SABA use was assessed in a higher proportion of patients (72.9% from 52.5%, p=0.026). - Higher proportion of patients received an asthma action plan (23.9% from 3.8%, p = 0.001), and asthma education (27.1% from 3.8%, p < 0.001).
Gentile 2003 USA, 14 months (2 baseline, 12 post-intervention)	Before-after study. ED of a tertiary hospital, 481 asthma patients. RoB: Serious (outcomes' selection and confounding).	Intervention: Introduction of an acute asthma protocol with specific criteria for diagnostic testing, aiming to safely reduce unneeded tests (chest x-rays and arterial blood gases). Control: Before.	- Unchanged hospital admission rate (19% from 20%) or hospital length of stay (3.12±1.6 from 3.83±2.8, p=0.26).	- 55% reduction in the number of chest radiographs (from 40% to 18%, p<0.001) - 57% reduction in the number of arterial blood gases (from 9.4% to 3.5%).
Goldberg 1998 USA, 25 months (6 baseline, 7 months interval, 9 post-intervention).	Before-after study. 1 ED, 246 asthma patients. RoB: Serious (outcomes' selection and confounding).	Intervention: Introduction of a critical pathway protocol for acute asthma assessment and management. Control: Before.	- No between group difference in the rate of hospitalizations or the number of endotracheal intubations.	- Decline in the use of oxygen by 19% (p=0.001), handheld nebulizer treatments by 33% (p=0.001), intravenous steroids by 13% (p=0.034) and saline locks by 15% (p=0.011). - Increase in the use of metered-dose inhalers with spacer by 64% (p=0.001) and oral steroids by 18% (p=0.027).

				- Non-significant trends over decreased ABG testing by 4% and lower length of ED stay (9%).
Joe 1992 USA, 14 months (3 baseline, 2 post intervention and 3 late follow-up, with intervals between them)	Before-after study. 1 ED, 350 asthma patients. RoB: Serious (outcomes selection and confounding).	Intervention: Introduction of an asthma care protocol, which was posted in the ED. Training included a 10-minute verbal presentation and three page summary of the literature. Control: Before		- No changes in treatment patterns were consistent both in short and later follow-up intervals
Lougheed 2009 Canada, 5 months.	Comparative cohort with concurrent and historical control. 10 EDs, 1262 asthma patients. RoB: Serious (outcomes' selection and confounding).	Intervention: Asthma care pathway including instructions, pre-printed physicians' orders, patient asthma action plan, a wall poster, and a pocket card. Implemented through peer-facilitated case-base workshops. Centres were encouraged to appoint champions. Control: No intervention/ Before		- Pathway use varied between 6-60% across centres. - Significant increase in ABG evaluation, use of bronchodilators by MDI, use of ICS and the use of oxygen, compared to control. Trend over increased use of systemic steroids. - Significantly increased reporting of PEFR, systemic steroids use and respiratory therapist's involvement in the care of patients when using the pathway. - No between group difference in the time to first bronchodilator and systemic steroid administration. - Significant decrease in PEFR documentation both in intervention and control centres.
Mackey 2007 Canada, 10 months (5 baseline, 5 post-intervention)	Before-after study. 1 ED, 141 asthma patients. RoB: Serious (outcomes' selection and confounding).	Intervention: A 4-page asthma care map for documenting history, PEFR medications, treatment, discharge instructions and nursing notes. Implementation through medical education and feedback to the ED staff. Control: Before.	- No significant differences in patients' outcomes within 48 hours. - There was a trend toward earlier relapses [within 48 hours] in the pre-intervention group (p=0.23)	- No change in the ED length of stay (2h25mins from 2h14mins). - Increase in the use of SABA during the first hour (median 3 vs 2, p=0.001) and during ED stay (median 4 vs 2, p=0.003). Increase in the use of SAMA during ED stay (medium 2 vs 1, p=0.0001). - No significant change in the prescription of discharge medications (ICS, OCS, prednisolone).
McFadden 1995 USA, 32 months (8 baseline, 24 post-intervention)	Before-after study. 1 ED, 1,513 asthma patients. RoB: Critical (participants' and outcomes' selection and confounding)	Intervention: Introduction of an asthma care pathway. Control: Patients treated without the protocol before or after the intervention period.	- Decrease in the number of hospital admissions by 27% and of ICU admissions by 41%. - Decrease in the frequency of return visits within 24 hours by 66%.	- Suboptimal use of PEFR for informing the decision for hospital admission or discharge. - The average time in the ED decreased by 50 minutes during the intervention period (p<0.001), but then rose again by an average of 16 minutes when protocol adherence diminished. In addition, the proportion of patients who stayed in ED for at least 3 hours decreased

			** During the last 12 months of the intervention, use of the pathway decreased and patients outcomes deteriorated.	(15% from 34%) during the intervention, but then increased to 47% again.
Robinson 1996 UK, 1 year (6 months baseline, 6 post-intervention)	Before-after study. 1 ED, 175 asthma patients. RoB: Serious (confounding)	Intervention: Introduction of a pre-printed, structured form for the assessment and management of acute asthma, following national guidelines and including prompts for demographic details, current symptoms, past medical history, physical examination, management, follow-up arrangements and discharge medications, according to severity. Control: Before.	- No significant differences in the admission rates (46% from 50%), or the rates of ED reattendance (0% from 3%)	- Significantly improved documentation of past asthma history (93% from 69%), usual medications (95% from 81%), respiratory rate (95% from 81%), predicted PEFR (75% from 23%), and percentage of predicted PEFR (62% from 1%). Significant decrease in the documentation of pulse rate (89% from 100%) and chest examination findings (91% from 100%). - Increased proportion of patients were treated in line with guidelines (89% from 50%) and had their inhaler technique checked (44% from 3%). - Less inappropriate discharges (28% from 54%). - No difference in the discharge prescriptions and follow-up plans.
Rowe 2008 Canada, 30 months (15 baseline, 15 post-intervention, 2 follow-up audits)	Before-after study. 1 ED, 387 patients. RoB: Serious (outcomes' selection and confounding)	Intervention: 4-page ACM developed by a multi-disciplinary team using evidence-based methods. Documentation of history, medications, physical findings, treatment, discharge instructions, PEFR, nursing notes. Control: Before.	- No impact in the proportion of patients admitted to the hospital (from 9% to 13% and 5%).	- Increasing use of oral steroids (75% and 68% versus 57% before, p<0.001, OR: 1.6 [1.0-2.7]) and earlier administration (<60 mins, p<0.01). - Decreasing use of supplemental oxygen (from 24% pre-intervention, to 21% and later 7%). - No change in the prescription patterns and timings of SABA and SAMA. - Increased time of ED stay from 181 pre-intervention to 209 and 265 mins, p <0.001). - Significant increase in oral steroids prescription at discharge (66% and 69% from 55%) and progressive decrease in the proportion discharged without any steroids (21% and 14% from 32%). Increased proportion discharged on ICS (OR: 3.4 [1.5-7.6]). - Care pathway was utilized in 67-70% of patients.
Steurer-Stey 2005 Switzerland, 6 years (19 months baseline, 3.5 years interval, 7	Before-after study. 1 urban ED, 311 asthma patients. RoB: Serious	Intervention: Asthma care pathway and local guideline. Training offered locally to the department. Control: Before		- Significantly increased respiratory rate reporting (65% from 14%), assessment of airway obstruction (96% from 53%), of pulse oximetry (84% from 24%). - Decreased frequency of ABGs (6% from 16%).

months post-intervention).	(participants' and outcomes' selection and confounding). ** Very long interval between the baseline and post-intervention measurements.			- Significant increase in the administration of systemic steroids (68% from 43%) in the ED and as discharge medications (70% from 37%); SABA upon arrival in the ER (96% from 88%), and in repeated SABA administration (84% from 31%). - Significant increase in PEFR use for evaluating treatment response (85% from 36%), in inhalers' technique documentation (14% from 5%).
Sukov 2000 USA, 3 months (1 baseline, 2 post-intervention)	Before-after study. 1 ED, 447 asthma patients. RoB: Moderate (confounding)	Intervention: 3-page care pathway developed through a modified- Delphi approach. Implemented after an educational session for all ED staff. Control: Before	- No significant improvement in the proportions of patients admitted to the hospital or the relapse rate.	- Significantly increased proportion of patients receiving 3 SABA doses within 90 minutes (86% from 63%). Significant decrease in ED length of stay (3.39±1.88 hours from 3.84±2.12 hours). - Trend towards increased use of PEFR on arrival (73% from 62%). - Care pathway was only utilized in 55% of patients in the intervention group.
Additional patient specific input by a specialized health professional				
Chew 2020 Singapore, 17 months.	Comparative observational study. 1 ED, 637 asthma patients. RoB: Serious (outcomes' selection and confounding)	Intervention: Afterhours respiratory nurse reviewed patients attending with acute asthma, offering a brief educational intervention, clinical decision support to emergency department physicians and audited clinical care. Control: Routine care without input by a respiratory nurse.		- Higher compliance with oral corticosteroids prescription, but not ICS prescription, in the intervention group. - More patients referred for follow-up review in the intervention group. - Low referral rate to the respiratory nurse by ED physicians.
Computer Decision Support Systems				
Kwok 2009 Australia, 14 months (7 baseline, 7 post intervention, with interval)	Before-after study. 1 ED, 100 patients. RoB: Serious (outcomes' selection and confounding).	Intervention: The Asthma Clinical Assessment Form and Electronic Decision Support (ACAFE), an online point of care clinical decision support system. Based on national asthma guidelines. Control: Before		- Significantly higher rates of documentation of asthma severity (98% from 18%), intensive care unit admission (90% from 14%), smoking history (98% from 64%), and asthma precipitants (94% from 66%). - Significantly higher rates of asthma management plan documentation (76% from 16%, $p<0.01$). - Trends over increased documentation of pulmonary function, smoking cessation advice and oral corticosteroids discharge prescription.

Introduction of a local or national guideline				
Pearson 1996 UK, 2 years (1 year baseline, 1 year post-intervention).	Audit. 36 teaching and district hospitals, 1,666 asthma patients. RoB: Serious (outcomes' selection and confounding)	Intervention: Introduction of a national asthma guideline. Control: Before		- Increase in the frequency that respiratory physicians administer a self-management plan (20% from 12%). No similar results in the non-specialists. No difference in the other seven standards that were assessed.
Medical education				
Veninga 1999 Netherlands, Norway, Sweden, Slovakia, 12 months.	Cluster RCT. 665 GPs. RoB: High (selection, performance, detection, reporting bias)	Intervention: Two educational meetings. Self-learning based on individual auditing and feedback of performance for small peer groups. Control: Educational intervention about a different disease (not asthma).		- No significant change in the proportion of patients receiving oral corticosteroids
Quality improvement process				
Akerman 1999 USA, 3.5 years (1 year baseline, 2.5 years intervention)	Comparative cohort with concurrent and historical control. Inner-city ED, 300 asthma patients. RoB: Moderate (confounding)	Intervention: Development of quality indicators (structure, process, outcome), auditing, training, introduction of new asthma encounter form. Personalized feedback and performance reports. Control: No intervention/ Before	- Decreased frequency of asthma relapse to 7.83% from 12.18% ($p<0.001$) and compared to the frequency of asthma relapse across the New York City Health Hospitals (12.79%). - Decreased asthma admission rate (3.90 from 4.85 per 100 ED visits, $p<0.02$).	
Chouaid 2004 France, 2.5 years intervention.	Before-after study. ED in a tertiary teaching hospital, 263 asthma patients RoB: Serious (outcomes' selection and confounding).	Intervention: Quality improvement program including auditing, local guidelines development, validation and distribution, staff training and feedback. Control: Before		- Significant improvement in the recording of recent medical history (100% from 68.7%), risk factors (100% from 63.5%), completion of the care pathway (94.5% from 27.8%). - Significantly improved documentation of the respiratory rate (81.8% from 36.5%), oxygen saturation (98.1% from 84.3%), and initial PEFR (98.1% from 19.1%). - Significantly improved prescription practices. - Follow-up was booked for a higher proportion of discharged patients (74.4% from 41.3%). - Significant increase in the documentation of drug prescriptions in the short term (85.1% from 67.3%), which however was not maintained 2 years later (41.9%).

Dalcin 2007 Brazil, 5 years (1 year baseline, 3 intervention, 1 post-intervention)	Before-after study. Adult ED, 500 asthma patients. RoB: Moderate (confounding).	Intervention: Development, validation, implementation and revision of a clinical pathway, annual audit, educational activities, and day to day progress monitoring. Control: Before.	- No effect on admission rate, ED discharge rate or death rate.	- Significant increase in pulse oximetry use (97% from 8.3%) and PEFR use (48% from 4.6%). However, the later decreased significantly during the last year, after discontinuation of the training process (29.7%). - Significant increase in the proportion of patients receiving three inhalations of treatment within the first hour (35.6% from 22.2%). - Significant increase in the use of oral versus IV corticosteroids (42.6% from 8.3%). - Reduction in the length of stay in the ED (8.4±10.1 hours from 12.4±17.0 hours, p= 0.04).
Doherty 2006 Australia, 14 months (7 baseline, 7 post-intervention)	Cluster RCT. 8 small rural hospitals, 187 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Quality improvement process based on the identification of evidence-practice gaps and barriers, guidelines development, reminders, education, audit and feedback. Control: No intervention.		- Significant increase in the proportion of patients whose asthma severity was assessed (62% from 8%), who had spirometry (62% from 12%), and those who received an asthma action plan (26% from 9%) and a trend over increased systemic steroid prescription (72% from 61%) in the intervention but not the control group. - Trend over decrease in the administration of ipratropium for mild asthma attacks (30% from 44%), in the intervention but not the control group. - Interestingly, a non-significant decrease in antibiotics prescription was observed in the control group (13% from 27%), with no change in the intervention group
Doherty 2007 Australia, 16 months (4 baseline, 12 post-intervention)	Comparative cohort with concurrent and historical control. 2 EDs in small rural hospitals, 215 asthma patients. RoB: Serious (outcomes' selection and confounding)	Intervention: Quality improvement process based on the identification of evidence-practice gaps and barriers, guidelines development, reminders, education, audit and feedback. Control: No intervention/ before.		- Significant increase in the proportion of patients whose asthma severity was assessed (99% from 27%), who had a spirometry or PEFR assessment (85% from 38%), who were offered an MDI with spacer (57% from 16%), those who received systemic corticosteroids (84% from 65%) and an asthma action plan (82% from 14%), in the intervention but not in the control hospital. - Significant decrease in the proportion of patients receiving SAMA for a mild exacerbation (16% from 43%) and in the proportion of patients receiving antibiotics (6% from 37%), in the intervention but not the control group.

				- Use of spirometry was increased both in the intervention (84% from 38%) and control hospital (40% from 2%).
Edmond 1998 USA, 1.5 year (6 months before, 12 during the intervention)	Before-after study. Urban teaching hospital, 196 asthma patients. RoB: Serious (confounding)	Intervention: Quality improvement process based on the identification of evidence-practice gaps and barriers, goal setting, guideline development and validation, education, reminders. Control: Before	- Progressively decreased hospital admission rate (19% from 35%, p<0.05). - No significant difference in the proportion of patients relapsing within 30 days from the ED visit (p=0.35)	- Median length of stay in the ED decreased by 58 minutes (p=0.01) and the proportion with a stay of less 4 hours increased consistently after the intervention (79% from 59%). - Significantly more patients had a baseline (83% from 20%) and follow-up (62% from 22%) PEFR measurement, while the median time until the first SABA was decreased from 22 to 6 minutes (p<0.001) - Median time until systemic corticosteroid administration did not change significantly.
Foster 2007 UK, 1 year.	Cluster RCT. 23 general practices, 545 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Quality improvement process including audits, practice development plans, multi-disciplinary training workshops and feedback of audit data. Control: Delayed implementation of the intervention (by 6 months).		- No difference in PEFR documentation at 6 months, but early intervention resulted in higher PEFR evaluation at 12 months (66% versus 36%, p<0.001). Gradual increase PEFR use over time in the intervention group (baseline: 15%, 6-months: 33%, 12-months 66%). The delayed group had a better baseline (44%) which did not improve over time. - Significant improvement of the adjusted, combined assessment scores at 12 months (p=0.02). - No significant differences in the combined management and follow-up scores.
Pinnock 2003 UK, 9 months (3 months baseline, 3 months post-intervention)	Before-after study. 4 primary care health centres, 258 asthma patients RoB: Serious (outcomes' selection and confounding)	Intervention: A quality improvement project including auditing and feedback, as well as an educational symposium and a workshop to facilitate multidisciplinary discussion. Control: Before		- General practices: Increase in the proportion of patients invited for follow-up (73% from 59%) and increased oxygen use (20% from 0%). - Out-of-hours services: Improved assessment of asthma attack severity (41% from 5%). - Nurse led walk-in clinic: PEFR more often compared with predicted value.
Stell 1996 UK, 14 months (2 months during the intervention, 1 10 months	Before-after study. 1 ED, 172 asthma patients. RoB: Serious (outcomes' selection, attrition and confounding)	Intervention: Continuous cycles of clinical audit. Results presented to staff, weaknesses discussed and methods for improvement were considered.		- Significant decrease in the use of nebulisers (88% from 97%), but consistent use of oral steroids. - Less patients had chest X-rays (43% from 73%), ABGs (33% from 73%) [these were recommended]. - Less patients had their inhaler technique checked (7% from 13%), were given PEFR meter (5% from 8%), were

interval, 2 months post-intervention)		Control: One year later, after the audit programme had ended and most medical staff had changed.		discharged on systemic steroids (when recommended, 53% from 63%), received follow-up plans (28% from 35%). - However, there was an increase in the regular treatment step-up, when required (34% from 20%).

* ABG: Arterial blood gases; ED: Emergency Department; PEFR: Peak expiratory flow rate

Table e7 Differences in the adherence to asthma guidelines by Specialists or Generalists.

Study	Design, Size, Quality	Clinical outcomes	Adherence outcomes
Diagnosis, assessment and maintenance treatment			
Abdulwadud 1999 Australia, 6 months. Specialists at the hospital vs GPs.	Single centre observational study. 1 tertiary hospital asthma clinic and nearby general practices, 105 asthma patients. RoB: Serious (outcomes' selection and confounding)		- Asthma knowledge was significantly higher among patients reviewed by GPs (p=0.002). - Patients reviewed by specialists had worse baseline quality of life, which however improved significantly during follow-up. Quality of life did not significantly improve among patients reviewed by GPs. However, there was no significant between group difference in quality of life change from baseline. - Patients seen by specialists significantly improved their self-management skills, in contrast to the control group. However, there was no significant between group difference.
Chou 2015 Taiwan, 10 years. Pulmonologists and allergists vs internists and GPs.	Longitudinal prescription trends and guidelines adherence analysis from a health insurance database. 4,495 asthma patients. RoB: Serious (outcomes' selection and confounding)		During the observation period, a steep increase was observed in the prescription of fixed dose combinations by asthma specialists (58.3% from 13.2%), which was significantly less pronounced among non-specialists. Moreover, specialists increasingly favoured inhaled over oral corticosteroids (70% from 50% of all patients received ICS and 20% from 30% were still receiving oral steroids). On the other hand, generalists prescribed ICS in only around 20% of their patients.
Erickson 2005 USA, ~2.5 years. Pulmonologists and allergists vs GPs.	Prospective observational cohort. One care organization, 4,742 asthma patients. RoB: Serious (confounding)	- Evaluation by a specialist after an acute asthma attack did not decreased future risk of asthma attacks. However, assessment by both an allergist and a pulmonologist was associated with reduced risk of subsequent ED visits for asthma (HR 0.37 [0.19-0.69]). - Evaluation by an allergist did not affect future hospitalization rate. However, review by a pulmonologist (HR: 0.74 [0.55-0.99]) or by both specialties (HR: 0.52 [0.29-0.93]) decreased future hospitalization rate.	

Frieri 2002 USA, 1 year. Allergists & immunologists vs primary care physicians,	Single centre audit. 1 University Hospital, 30 asthma patients. RoB: Serious (outcomes' selection and confounding)		- Allergists & immunologists prescribed more ICS (100% vs 80%) and had a lower LABA to ICS use ratio (0.83 vs 1.60, indicative of higher guideline adherence). - Allergists & immunologists diagnosed allergic rhinitis more frequently (80% vs 13%) and performed skin testing to identify allergy triggers in all patients (100% vs 0%). - Allergists & immunologists obtained PEFR values for all their patients (100% vs 0%). They performed spirometry for more patients (14/15 vs 9/15).
Harmsen 2010 Denmark, 3 years. Pulmonologists vs GPs	RCT. 308 asthma patients, 1 General Hospital. RoB: High (randomization [unclear], concealment, blinding, attrition bias)	- Asthma severity scores were more frequently unchanged or worse in GP vs pulmonologists groups (67% vs 45%, p<0.01). Rhinitis symptoms were similar between groups. - AQLQ and RQLQ scores were significantly improved in the pulmonologists group compared to baseline and compared to GPs, but the change did not exceed MCID. - Unchanged lung function measurements at 3-year follow-up visit in both groups.	
Kanter 2002 USA, 1 year Allergists vs GPs	Observational study. 2 allergy and 2 general practices, 119 asthma patients. RoB: Serious (confounding)	- Patients reviewed by allergists reported improved health related quality of life in all SF-36 domains. In five SF-36 domains, the change from baseline was significant higher for patients reviewed by allergists vs GPs (role-physical, bodily pain, general health perceptions, vitality and social functioning, P<0.05). - Review by allergist was also associated with statistically significantly higher mean improvement from baseline in the symptom-free index, functioning with asthma, asthma energy scales and total score of the ITG asthma short form. - No between group differences in the number of physician visits or hospitalizations.	- Patients treated by allergists were receiving more often oral or nasal/ inhaled corticosteroids/ anti-inflammatories.

Meng 1999 USA. Asthma Specialists vs generalists.	Cross-sectional study. 8 health regions in 7 states, 6703 asthma patients RoB: Serious (participants' selection, confounding)	- Under specialists care, more patients receive <8puffs of inhaler per day (1.25, p<0.05).	- Regular use of inhaled steroids is prescribed more frequently by specialists (OR: 2.57, p<0.01). - Under specialists' care, more patients measure their peak flow regularly (OR 4.83, p<0.01) and had an allergy evaluation (OR: 3.16, p <0.01)
Morishima 2011, Japan. Pullmonologists or allergists vs non-specialists	Cross-sectional study. Insurance claims database in Kyoto, 13,428 asthmatics. RoB: Low		- Specialists were more likely to prescribe ICS (aOR: 2.70, [2.46-2.97].
Schayck 1989 Netherlands. Pulmonologists vs GPs	Cross-sectional study. 29 general practices, 233 asthma patients. RoB: Serious (outcomes' selection and confounding)		- Pulmonologists prescribed six time more ICS than GPs. In general, they prescribed more medications that GPs. - Pulmonologists prescribed higher doses of ICS for more severe asthma, while GPs prescribed more bronchodilators. - 20% and 16% of those treated by pulmonologists or GPs, received treatments for which they did not respond, at least at the time of testing.
Tada 2015 Japan. Pulmonologists vs GPs	Cross-sectional study. 39 private clinics and 9 general hospitals. 860 asthma patients. RoB: Serious (confounding)	- Older patients with more severe asthma (GINA 3-5) and younger patients under the care of pulmonologists achieved better disease control (ACT, p=0.048), compared to those treated by GPs. - Older patients with milder asthma (GINA 1-2) under the care of GPs achieved better control. - Elderly asthmatics under the care of GPs used fewer rescue inhalers compared to those treated by pulmonologists. However, those treated by GPs had in general less severe disease and the study results were not adjusted.	
Vollmer 1997 USA.	Cross-sectional study.	- Allergists' patients had improve quality of life as measured by several dimensions of the SF-36 scale (p <0.05).	- Patients receiving primary asthma care by allergists were more often using inhaled anti-inflammatory agents, oral

Allergists vs GPs.	1 Health maintenance organization (Kaiser Permanente, Portland). 914 asthma patients RoB: Serious (confounding, attrition bias).		steroids and regular inhaled medications to control their asthma (p<0.01). - Allergists' patients were more likely to have asthma exacerbations treated in a clinic setting rather than the emergency department (p<0.01).
Wu 2001 USA, 2 years. Pulmonologists, Allergists or experienced generalists vs generalists	Cohort study 12 managed care organizations, 1,078 physicians, 1,954 asthma patients. RoB: Serious (confounding)	- Overall, specialists or experienced generalists care was associated with less ED visits, hospitalisations and missed days of work. - Patients under the care of pulmonologists specifically, had more hospitalizations, but reported better quality of asthma care, suggesting the increased hospitalization may result from a more severe asthma.	- Specialists and experienced generalists more often offered allergy evaluation, peak flow meter at home, prescribed ICS and oral corticosteroids, discussed asthma triggers and offered asthma education. - On the other hand, these patients were more often overusing SABAs.
Zeiger 1991 USA. 6 months follow-up. Asthma specialists vs general physicians.	RCT. 1 Health maintenance organization (Kaiser Permanente, San Diego). 309 asthma patients. RoB: High (selection, performance, detection bias).	Management by asthma specialist was associated with: - 75% reduction in night awakenings (p<0.001). - Almost 50% reduction in asthma attacks leading to an emergency presentation (p=0.017). - Reduction in the frequency of asthma attacks (p = 0.005)	- Inhaled corticosteroids (p<0.001) and cromolyn (p=0.002) were prescribed more often by asthma specialists compared to control.
Diagnosis, assessment and management of acute attacks			
Bell 1991 UK, 2 years. Pulmonologists vs internists.	Single centre audit. 76 asthma patients, 1 district general hospital. RoB: Serious (outcomes' selection and confounding)		- Prescription patterns: Chest physicians administered emergency treatments (SABA & systemic steroids) more often within the target timeframe, and tailored treatment to response more effectively. There were no between-group differences in antibiotic prescription practices. - Specialists organized OPD follow-up more frequently. Specialists recorded severity measures more accurately.
Pearson 1996 UK, 2 years.	Audit. 36 teaching and district hospitals, 1,666 asthma patients.		- Pulmonologists were more likely to assess pCO2 on arrival, to prescribe systemic steroids within 24 hours from presentation, to assess PEFR variability, to prescribe oral steroids on discharge, to organize an outpatient

Pulmonologists vs general physicians.	RoB: Serious (outcomes' selection and confounding)		appointments, and to provide a self-management plan (p<0.05).
Pellicer 2001 Spain. Pulmonologists vs GPs	Cross-sectional study. 96 outpatients that have been assigned an asthma diagnosis by a pulmonologist or GP. RoB: Low	- Diagnosis by a pulmonologist did not significantly differ from the final diagnosis based on rigorous evaluation of clinical characteristics and relevant laboratory tests / biomarkers. However, GP diagnosis differed significantly from the final diagnosis.	

* GPs: General practitioners, OPD: Outpatient department, PEFR: Peak Expiratory Flow Rate.

ERS/EAACI statement on adherence to international adult asthma guidelines

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Online Supplement

Contents:

- **Survey Questionnaires**

T2 Mild Asthma

A 22 year-old female, non-smoker, maths student attends for a consultation in October complaining about occasional chest tightness and cough (especially when playing tennis), during late spring to mid summer the last 4 years. She has never used any inhalers for her chest symptoms. Regular chest auscultation provides you with normal lung sounds.

She also mentions that during the same months she has been experiencing watery eyes and nose, nasal congestion as well as sneezing. These symptoms began early at adolescence and have been managed with as needed, over the counter antihistamines. She was diagnosed with eczema and egg allergy as a toddler with both conditions having resolved by the age of 10 years, which was the age she was last evaluated in an allergy clinic. She has a cat at home.

1st Question: What are your thoughts on your patient's health condition? (one answer applies)

1. the history of the symptoms from the lower respiratory system are typical of asthma and I can thus set the diagnosis of asthma for this patient
2. the history of the symptoms from the lower respiratory system are not typical of asthma and I need to focus on the treatment of the nasal symptoms
3. the history of the symptoms from the lower respiratory system are indicative of asthma but I need to check whether there is variable expiratory flow limitation
4. the history of the symptoms from the lower respiratory system are indicative of asthma but I need to check whether there is variable inspiratory flow limitation

2nd Question: Which of these investigations would you decide to perform/order if all were available to you? (more than one answer can apply)

- Spirometry, Bronchodilator test
- Peak flow, Bronchodilator test
- FeNO
- blood eosinophilia
- total serum IgE
- Skin prick test to common aeroallergens
- Specific serum IgE
- Chest X-Ray
- ENT examination
- Bronchoscopy
- Bronchoprovocation test
- Bacteriological exam of the sputum
- Detailed history
- Chest auscultation with fierce exhalation
- Home peak flow monitoring, including before and after playing tennis

3rd Question: Chest auscultation with fierce exhalation provides normal sounds. You had the possibility of performing spirometry and received the following outcomes: baseline spirometry resulted in FEV1/FVC ratio 0.75 and administration of 400 mcg salbutamol increased FEV1 by 10% (150 ml). What is your diagnosis and how would you manage the patient?

1. I have excluded that the patient has asthma and will discharge her by prescribing treatment for the nasal symptoms during Spring/Summer.
2. I have excluded that the patient has asthma, I will prescribe treatment for the nasal symptoms during Spring/Summer and will rebook the patient to come back in June.
3. I have not excluded that the patient has asthma, and will teach her to monitor her peak flows both when she has symptoms and when she is asymptomatic. I will rebook the patient to come back in June for lung function testing.
4. The diagnosis of asthma is certain and I will prescribe a reliever to be used during the pollen season together with the rhinitis treatment.

The patient comes back during the pollen season. She reports episodes of chest tightness and cough especially early in the morning when she is walking to work through a park and if walking back home late evening. She additionally mentions wakening up at night due to chest tightness and nasal blockage. She has been avoiding playing tennis because of these symptoms. She is receiving her antihistamine daily but no nasal spray. Regular chest auscultation provides you with normal lung sounds. Spirometry with reversibility results in 13% (220 ml) increase in FEV1 post the bronchodilator administration.

4th Question: What is the level of asthma control?

- **A.** Controlled
- **B.** Partially controlled
- **C.** Uncontrolled

5th Question: Which is the asthma severity level?

- **A.** Moderate persistent
- **B.** Severe persistent
- **C.** Mild persistent
- **D.** Intermittent
- **E.** Mild intermittent
- **F.** Moderate intermittent
- **G.** Severe intermittent

FeNO is 38 ppb. Skin prick testing with common aeroallergens elicited positive response of 9mm wheal to grass pollen mix. Blood eosinophils 210/cml

6th question: Which is the phenotype? (multiple answers can apply)

A. Type 1
B. Type 2
C. Mixed type 1 and 2
D. Allergic asthma
E. Asthma with allergic sensitization
Z. I do not know

7th Question: How would you manage the patient?

1. I will step up with her nasal treatment only
2. In addition to the nasal therapy, I will prescribe reliever treatment for her asthma to be used at pollen season.
3. In addition to the nasal therapy, I will prescribe inhaled steroids for her asthma to be used regularly according to her asthma action plan which will advise her a) what action to take if the symptoms worsen, b) how to reduce/stop the dose as symptoms resolve at the end of the pollen season and c) how to recommence treatment if/when symptoms recur. I will review her again next year, at pollen season when I know she is expected to have symptoms.
4. In addition to the nasal therapy, I will prescribe inhaled corticosteroids (ICS) to be received until symptoms disappear and will review her again next year towards the end of Spring when I know she is expected to have symptoms

8th Question: If you choose to prescribe asthma treatment, what would that be? (multiple answers can apply)

1. Low dose ICS
2. Montelukast
3. Low dose ICS/LABA
4. Moderate/high ICS dose
5. Salbutamol twice daily
6. LABA
7. Omalizumab
8. AIT

T2 Severe Asthma

A 21 year-old male, BMI=23, comes for a consultation due to coughing, shortness of breath and wheezing. He has been suffering with asthma since childhood; from 3-12 years of age he was treated with inhaled budesonide, later on with fluticasone/salmeterol 50/250 dry powder inhaler, 1 puff twice-daily, while the last 4 years with fluticasone/salmeterol 50/500 dry powder inhaler, 1 puff twice-daily. Despite this treatment, he suffers from night symptoms twice a week which prompt him to use salbutamol. Playing football or cyclying also cause asthma exacerbation especially during Spring. He complains of itchy eyes and nose, sneezing and runny nose all year round but worse during springtime. He uses loratadine on demand for his nasal and ocular symptoms.

He is a student in journalism, with no exposure to chemicals or other substances and doesn´t smoke. He lives in a house with a tree-garden in a small town, and does not keep pets.

1st question: Which of these investigations would you decide to perform/order if all were available to you? (multiple answers possible)

A) Spirometry, Bronchodilator test
B) Peak flow, Bronchodilator test
C) FeNO
D) blood eosinophilia
E) total serum IgE
F) Skin prick test to common aeroallergens
G) Specific serum IgE
H) Chest X-Ray
I) ENT examination
J) Bronchoscopy
K) Bronchoprovocation test
L) Bacteriological exam of the sputum
M) Detailed history
N) Chest auscultation
O) Serial peak flow readings
P) Check his prescribing record and discuss adherence
Q) Assess inhaler technique

Spirometry shows baseline FEV1=3.49l (76.3% of predicted), with a bronchodilator reversibility test of 28% (250ml).

2nd Question: What is the level of asthma control?

- **A.** Controlled
- **B.** Partially controlled
- **C.** Uncontrolled
- **D.** I do not know

3rd Question: Which is the asthma severity level?

- **A.** Moderate persistent
- **B.** Severe persistent
- **C.** Mild persistent
- **D.** Intermittent
- **E.** Mild intermittent
- **F.** Moderate intermittent
- **G.** Severe intermittent
- **H.** I do not know

4th Question: What would you do next (more than one answers can apply)?

- **A.** Step up treatment according to GINA recommendations
- **B.** Maintain the same treatment
- **C.** Step down because there are no activity limitations
- **D.** Investigate patient's adherence
- **E.** Evaluate the presence of comorbidities
- **F.** Evaluate inhaler technique
- **G.** Investigate the asthma phenotype

The patient has asthma symptoms when exercising outdoors during late Spring. FeNO at this time point is 113 ppb. Blood eosiniphils 500/cml and Skin prick tests are positive to grass and tree pollen, and Alternaria mold.

5th Question: Which is the phenotype? (multiple answers can apply)

- A. Type 1
- B. Type 2
- C. Mixed type 1 and 2
- D. Allergic asthma
- E. Asthma with allergic sensitization
- F. I do not know

6th Question: Is he under risk of exacerbations?

A. Yes

B. No

7th Question: Indicate the risk factors (multiple answers can apply):

A. Allergen exposure

B. Uncontrolled rhinitis

C. Blood eosinophilia

D. Impaired lung function

E. Elevated FeNO

F. Food allergy

G. Night time awakenings

H. High doses of ICS

I. Obesity

J. Aspirin sensitivity

8th question: Which would be your preferred option to control his asthma (multiple answers can apply)?

A. Tiotropium

B. Omalizumab

C. Oral corticosteroids

D. Montelukast

E. Anti-IL 5

F. Anti-IL4/13

G. Change ICS to fine particles ICS

H. Phosphodiesterase 4 (PDE4) inhibitors

I. Increase ICS dose

J. Rhinitis treatment

K. Allergen immunotherapy

9th Question: The patient returns for follow up. What tests would you choose to perform to investigate asthma control (multiple answers can apply)?

A. Asthma control test
B. Lung function with bronchodilator
C. Fe NO
D. Blood eosinophils
E. Specific IgE
F. Chest X-Ray
G. High Resolution CT scan

10th Question: Asthma control is not achieved. Which would be your preferred option as a second step? (multiple answers can apply)

A. Tiotropium
B. Omalizumab
C. Oral corticosteroids
D. Montelukast
E. Anti-IL 5
F. Anti-IL4/13
G. Change ICS to fine particles ICS
H. PD4 inhibitors
I. Increase ICS dose
J. Rhinitis treatment
K. Allergen immunotherapy
L. Referral to a Specialist/Difficult Asthma Clinic

Non T2 asthma

A 50 year-old lady attends as an emergency due to breathlessness. She reports that her dyspnea has worsened over the last two weeks despite using 2 puffs of beclomethasone dipropionate/formoterol (100/6 μg) twice daily and that she now needs to use her reliever (salbutamol) four times a day. On presentation, she talks in phrases but wheezes, her oxygen saturation is 92%, pulse rate at 118bpm, respiratory rate at 28bpm, FEV_1 72% pred., FVC 82% pred., FEV_1/FVC 0.68 while electrocardiography is unremarkable. She was diagnosed with asthma 10 years ago (PC20 for methacholine <4 mg/ml), skin prick testing to common aeroallergens was negative. Since then she has been on high doses of inhaled corticosteroids but often uses salbutamol after exercise and sometimes during the night. She has to take oral corticosteroids around 4 times a year for asthma exacerbations and was hospitalized due to asthma twice in the last 5 years (once at ICU). She is 160 cm tall, weighs 90 kg, works in a dye-factory and has been occasionally smoking the last 30 years.

1st Question: How would you manage the patient? (multiple answers can apply)

A) Hospitalize the patient immediately due to life-threatening asthma exacerbation.
B) Give 1 mg/kg intravenous prednisolone, controlled oxygen, 4-10 puffs of salbutamol and re-evaluate after 1 hour.
C) Give 50 mg intravenous prednisolone, controlled oxygen, 4-10 puffs of salbutamol and re-evaluate after 1 hour.
D) Give 1 mg/kg prednisolone by mouth, controlled oxygen, 4-10 puffs of salbutamol and re-evaluate after 1 hour.
E) Give 50 mg prednisolone by mouth, controlled oxygen, 4-10 puffs of salbutamol and re-evaluate after 1 hour.
F) Prescribe oral prednisolone 50 mg/day, send home and review response after 1 week.
G) Prescribe oral prednisolone 1 mg/kgr, send home and review response after 1 week.
H) Advise using ICS/formoterol also as a reliever (maximum 72 μg formoterol) and review response after 2 days.

2nd Question: The patient attends the follow-up consultation. Which of the following investigations would you decide to perform/order if all were available to you? (more than one answer can apply)

- Spirometry, Bronchodilator test
- Peak flow, Bronchodilator test
- FeNO
- blood eosinophilia
- total serum IgE
- Skin prick test to common aeroallergens
- Specific serum IgE
- Chest X-Ray
- ENT examination

- Bronchoscopy
- Bronchoprovocation test
- Bacteriological exam of the sputum
- Detailed history
- Chest auscultation
- Occupational exposure evaluation
- Check her prescribing record and discuss adherence
- Check inhaler technique

Spirometry results are as following: FEV1 79% pred., FVC 82% pred., FEV1/FVC 0.72, reversibility 7% (150ml). Chest auscultation normal. She still needs to use her reliever at least three times a week.

3rd Question: What is the level of asthma control?

E. Controlled
F. Partially controlled
G. Uncontrolled
H. I do not know

4th Question: Which is the asthma severity level?

I. Moderate persistent
J. Severe persistent
K. Mild persistent
L. Intermittent
M. Mild intermittent
N. Moderate intermittent
O. Severe intermittent
P. I do not know

FeNO is 6 ppb. Skin prick testing with common aeroallergens is negative. Blood eosinophils 48/cml.

5th Question: Which is the phenotype? (multiple answers can apply)

A. Type 1
B. Type 2
C. Mixed type 1 and 2
D. Allergic asthma
E. Asthma with allergic sensitization
F. Occupational asthma
G Related to her obesity
H. Asthma COPD overlap syndrome

I. I do not know

6th Question: How should the patient be managed on a long term? (multiple answers can apply)

A) There is no need to change medications.
B) Advise using ICS/formoterol as maintenance and as reliever (maximum 72 µg formoterol).
C) Add leukotriene receptor antagonist to moderate/high dose ICS/LABA bi-daily
D) Add tiotropium to moderate/high dose ICS/LABA twice daily
E) Advise taking 250 mg azithromycin 3 times a week for 3 months.
F) Change of work place
G) Anti-IL5
H) Anti-IL4/13
I) Omalizumab
J) Allergen Immunotherapy
K) Phosphodiesterase 4 (PDE4) inhibitors
L) Bronchial thermoplasty
M) Provide self-management education including an action plan

7th Question: After stepping up in the treatment, the patient still complaints of frequent need of reliever use. How would you proceed? (more than one answer can apply)

A) Re-evaluate the initial diagnosis
B) Assess for comorbidities
C) Assess adherence to treatment
D) Assess inhaler use technique
E) Prescribe regular low dose oral corticosteroids (7.5 g/day).
F) Advise smoking cessation and weight reduction.
G) Psycho-social assessment
H) Pulmonary rehabilitation

- **Search strategy**

Search 1: Systematic review of studies evaluating interventions aimed to improve adherence to asthma guidelines.

#1	Asthma[MH]
#2	Asthma[tiab]
#3	Asthma*[tiab]
#4	Anti-Asthmatic Agents[MH]
#5	#1 or #2 or #3 or #4
#6	Guideline[MH]
#7	Evidence-Based Medicine[MH]
#8	practice guidelines as topic[MH]
#9	Guideline[tiab]
#10	Guideline*[tiab]
#11	Guidance[tiab]
#12	#6 or #7 or #8 or #9 or #10 or #11
#13	Quality improvement[mh]
#14	Patient care planning[mh]
#15	Guideline adherence[mh]
#16	Outcome and Process Assessment (Health Care) [mh]
#17	Decision Support Systems, Clinical[mh]
#18	Comprehension[mh]
#19	Audit[tiab]
#20	Quality[tiab] and (improvement[tiab] or (improve*[tiab]))
#21	(guideline[tiab] or (guidance[tiab]) or (guideline*[tiab]) or (guida*[tiab])) and (adherence[tiab])
#22	Decision support[tiab]
#23	Understanding[tiab]
#24	Implement*[tiab]
#25	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#5 and #12 and #25

#27	(child[mh]or (adolescent[mh])) not (adult[mh])
#28	animals[mh] not (humans[mh])
#29	letter[publication type]
#30	editorial[publication type]
#31	review[publication type]
#32	systematic review [publication type]
#33	systematic[tiab] and (review[tiab])
#34	meta-analysis[tiab]
#35	metaanalysis[tiab]
#36	#31 NOT (#32 or #33 or #34 or #35)
#37	#26 not (#27 or #28 or #29 or #30 or #36)

Search 2: Studies assessing differences in the process and clinical outcomes in patients managed by Specialists versus Generalists.

#1	Asthma[MH]
#2	Asthma[tiab]
#3	Asthma*[tiab]
#4	Anti-Asthmatic Agents[MH]
#5	#1 or #2 or #3 or #4
#6	Referral and consultation[MH]
#7	Referral[tiab]
#8	Medical specialties [MH]
#9	specialist[tiab] or specialty[tiab]
#10	respiratory[tiab]
#11	pulmonary[tiab]
#12	allergy [tiab]
#13	allergist [tiab] or pulmonologist [tiab] or pulmonology [tiab]
#14	#9 or #10 or #11 or #12 or #13
#15	(#7 or #8) and #14
#16	#6 or #15

#17	#5 and #16
#18	(child[mh]or (adolescent[mh])) not (adult[mh])
#19	animals[mh] not (humans[mh])
#20	letter[publication type]
#21	editorial[publication type]
#22	review[publication type]
#23	systematic review [publication type]
#24	systematic[tiab] and (review[tiab])
#25	meta-analysis[tiab]
#26	metaanalysis[tiab]
#27	#22 NOT (#23 or #24 or #25 or #26)
#28	#17 not (#18 or #19 or #20 or #21 or #27)

Table e1 Results from the questionnaire survey – Mild T2 asthma (%). *P-values pertain to comparisons among the three groups, using chi-squared test.

	Allergy doctors (n=141)	**Respiratory doctors (n=542)**	**Generalists (n=78)**	P-value*
What is your diagnosis and how would you manage the patient?				
Excluded asthma discharge	1.4	0.9	1.3	
Excluded asthma rebook	2.1	1.5	6.4	0.06
Not excluded asthma	76.6	83.8	75.6	
Diagnosed asthma	19.9	13.8	16.7	
What is the level of asthma control?				
Controlled	2.9	1.5	4.0	
Partially controlled	21.3	16.9	21.3	0.29
Uncontrolled	75.7	81.6	74.7	
Which is the asthma severity level?				
Intermittent	8.1	9.0	8.0	
Mild intermittent	9.6	9.0	12.0	
Mild persistent	16.9	16.1	12.0	
Moderate intermittent	27.9	23.6	33.3	P=0.37
Moderate persistent	32.4	31.0	28.0	
Severe intermittent	0.7	5.8	1.3	
Severe persistent	4.4	5.6	5.3	
Which is the phenotype?				
Type 1	6.6	8.6	5.3	0.51
Type 2	30.2	13.6	1.3	<0.0001
Mixed type 1 and 2	1.5	5.6	10.7	0.02
Allergic asthma	79.4	61.7	56.0	<0.0001
Asthma with allergic sensitisation	33.8	34.3	46.7	0.10
Don't know	2.9	9.2	14.7	0.01
How would you manage the patient?				
Step up nasal only	0.8	0.8	1.3	
Reliever in addition	9.5	10.9	12.0	
ICS in addition + asthma action plan	882	85.6	84.0	0.91
ICS in addition + follow up	1.5	2.7	2.7	
If you choose to prescribe asthma treatment, what would that be?				
Low ICS	36.8	35.4	44.0	0.35
Montelukast	40.4	37.2	32.0	0.48
Low ICS+LABA	55.8	55.9	44.0	0.14
Moderate-High ICS	16.9	16.1	14.7	0.91
SABA twice daily	8.8	5.2	10.7	0.09
LABA	7.4	5.9	4.0	0.61
Omalizumab	2.9	1.5	4.0	0.27
AIT	48.5	6.7	2.7	<0.0001

Table e2 Results from the questionnaire survey – Severe T2 asthma (%). *P-values pertain to comparisons among the three groups, using chi-squared test.

	Allergy doctors (n=99	**Respiratory doctors (n=361)**	**Generalists (n=47)**	P-value*
What is the level of asthma control?				
Don't know	1.0	3.3	4.3	
Controlled	1.0	0.3	2.2	0.53
Partially controlled	26.3	22.4	21.2	
Uncontrolled	71.7	74.0	72.3	
Which is the asthma severity level?				
Intermittent	1.0	0.8	2.1	
Mild intermittent	1.0	3.3	4.3	
Mild persistent	4.0	6.4	6.4	
Moderate intermittent	3.0	3.6	4.3	0.66
Moderate persistent	43.4	46.0	44.7	
Severe intermittent	2.0	1.9	0	
Severe persistent	41.4	37.4	36.2	
Don't know	2.0	0.3	2.1	
What would you do next				
Step up treatment according to GINA	74.8	76.7	66.0	0.27
Maintain the same treatment	2.0	3.6	2.0	0.41
Step down because there are no activity limitations	0	0.6	2.1	0.29
Investigate patient's adherence	91.9	87.8	83.0	0.27
Evaluate the presence of comorbidities	91.9	76.4	66.0	<0.0001
Evaluate inhaler technique	98.0	90.9	89.4	0.051
Investigate the asthma phenotype	77.8	68.1	61.7	0.09
Which is the phenotype?				
Type 1	5.0	12.5	12.8	0.10
Type 2	31.3	19.4	10.6	0.007
Mixed type 1 and 2	16.2	15.5	10.6	0.65
Allergic asthma	71.7	57.1	46.8	0.007
Asthma with allergic sensitisation	36.4	31.6	29.8	0.62
Don't know	3.0	10.0	23.4	0.001
Is he under risk of exacerbations?				
Yes	99.0	94.5	91.5	
No	0	1.9	4.3	0.24
Don't know	1.0	3.6	4.3	
Indicate the risk factors				
Allergen exposure	89.9	80.1	80.8	0.08
Uncontrolled rhinitis	68.7	64.0	66.0	0.68
Blood eosinophilia	50.5	58.2	48.9	0.24
Impaired lung function	50.5	51.0	42.6	0.55
Elevated FeNO	53.5	61.5	51.1	0.18
Food allergy	11.1	11.9	10.6	0.95
Night time awakenings	63.6	68.7	60.0	0.34
High dose of ICS	36.4	41.8	40.4	0.62
Obesity	25.2	17.2	14.9	0.15
Aspirin sensitivity	14.1	13.3	10.6	0.84

Which would be your preferred option to control his asthma?				
Tiotropium	20.2	46.5	19.2	<0.0001
Omalizumab	30.3	21.0	23.4	0.15
Oral corticosteroids	21.2	16.3	10.6	0.26
Montelukast	54.6	59.8	48.9	0.28
Anti-IL 5	18.2	14.1	10.6	0.43
Anti IL4/13	5.0	3.3	0	0.28
Change ICS to ultra-fine particle ICS	25.2	34.1	27.7	0.20
Phosphodiesterase 4 inhibitors	1.0	1.7	0	0.62
Increase ICS dose	43.4	31.9	31.9	0.09
Rhinitis treatment	75.8	71.2	63.8	0.32
Allergen immunotherapy	50.5	24.1	36.2	<0.0001
. What tests would you choose to perform to investigate asthma control?				
Asthma control test	88.9	85.6	78.7	0.26
Lung function with bronchodilator test	78.8	79.8	74.5	0.70
FeNO	73.7	69.5	53.2	0.04
Blood eosinophils	37.4	44.0	29.8	0.12
Specific IgE	22.2	19.7	14.9	0.58
Chest X-ray	9.1	10.5	8.5	0.86
High resolution CT scan	6.1	5.5	4.3	0.90
Which would be your preferred option as a second step?				
Tiotropium	3.0	8.0	10.6	0.02
Omalizumab	27.3	21.0	8.5	
Oral corticosteroids	13.1	9.1	6.4	
Montelukast	5.0	5.3	4.3	
Anti-IL 5	20.2	15.8	8.5	
Anti IL4/13	2.0	2.5	0	
Change ICS to fine particle ICS	3.0	5.3	6.4	
Phosphodiesterase 4 inhibitors	0	0.6	0	
Increase ICS dose	5.0	5.0	8.5	
Rhinitis treatment	1.0	1.7	2.1	
Allergen immunotherapy	6.0	1.7	0	
Referral to Specialist/ Difficult Asthma Clinic	13.1	19.9	40.4	

Table e3 Results from the questionnaire survey – Non T2 asthma (%). *p-values pertain to comparisons among the three groups, using chi-squared test.

	Allergy doctor (n=205	**Respiratory doctors (n=338)**	**Generalists (n=134)**	P-value*
How would you manage the patient at the emergency department?				
Hospitalisation	23.4	26.6	19.4	0.24
Prednisolone 1mg/kg iv	29.3	21.6	15.7	0.01
Prednisolone 50 mg iv	16.6	23.4	9.7	0.002
Prednisolone 1 mg/kg po	16.6	9.5	13.4	0.047
Prednisolone 50mg po	17.6	24.6	26.1	0.10
Prednisolone 50 mg/day	9.8	8.9	11.9	0.60
Prednisolone 1 mg/kg/day	4.4	4.1	3.7	0.96
ICS/Formoterol as reliever	20.5	18.3	17.9	0.78
What is the level of asthma control?				
Controlled	1.3	1.1	3.3	
Partially controlled	45.7	47.6	34.4	0.16
Uncontrolled	53.0	49.4	60.0	
Don't know	0	1.9	2.3	
Which is the asthma severity level?				
Intermittent	0.7	1.1	2.2	0.88
Mild intermittent	1.3	1.9	2.2	
Mild persistent	6.6	11.5	8.9	
Moderate intermittent	2.0	2.2	3.3	
Moderate persistent	43.7	41.3	37.8	
Severe intermittent	2.6	3.7	6.7	
Severe persistent	40.0	35.3	35.6	
Don't know	3.3	3.0	3.3	
Which is the phenotype?				
Type 1	25.2	19.0	7.8	0.004
Type 2	9.9	19.0	5.6	0.002
Mixed type 1 and 2	12.6	13.0	15.6	0.79
Allergic asthma	5.3	4.1	7.8	0.38
Asthma with allergic sensitisation	0	1.9	10.0	<0.0001
Occupational asthma	29.8	34.9	23.3	0.11
Obesity related	58.3	54.3	37.8	0.006
Asthma COPD overlap	41.1	30.1	30.0	0.06
Don't know	4.6	10.8	25.6	<0.0001
How should the patient be managed on a long term?				
ICS/LABA smart	55.0	56.9	62.2	0.54
Montelukast	51.7	41.6	36.7	0.046
Tiotropium	65.6	73.2	57.8.0	0.02
Azithromycin	13.2	11.9	4.4	0.08
Occupation change	36.4	40.5	31.1	0.26
Ant IL-5	20.5	9.7	3.3	<0.0001
Anti IL-4/13	4.0	2.2	1.1	0.35
Anti IgE	11.9	4.8	3.3	0.008
AIT	4.6	1.1	4.4	0.06
Roflumilast	3.3	2.2	3.3	0.75

Bronchial thermoplasty	3.3	4.5	0	0.12
Education	72.9	72.5	71.1	0.96
After stepping up in the treatment, the patient still complaints of frequent need of reliever use. How would you proceed?				
Re-evaluation of diagnosis	75.5	72.9	80.0	0.39
Assess comorbidities	93.4	89.2	83.3	0.049
Check adherence	94.0	93.7	84.4	0.01
Check inhalation technique	94.0	95.9	88.9	0.05
Oral corticosteroids	24.5	17.1	24.4	0.12
Smoke cessation	94.0	95.2	91.1	0.37
Psycho social assessment	59.6	61.3	57.8	0.82
Pulmonary rehabilitation	36.4	50.6	52.2	0.01

Table e4 Risk of bias of the included studies (a) Randomized controlled trials; (b) Observational studies.

a.

Studies	Random sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other source of bias
Armour 2007	H	H	H	H	L	L	L
Herborg 2001	H	H	H	H	L	L	L
Manfrin 2017	H	H	H	H	L	L	L
McLean 2003	H	H	H	H	L	L	L
Pilotto 2004	H	H	H	H	L	L	L
Premaratne 1999	H	H	H	H	H	L	L
Wong 2017	H	H	H	H	H	L	L
Zeiger 2014	L	L	H	H	L	L	L
Renzi 2006	L	L	L	L	H	L	L
Eccles 2002	H	H	H	H	H	L	L
Kuilboer 2006	H	H	H	H	L	H	L
Martens 2007	H	H	H	H	L	H	L
McCowan 2001	H	H	H	H	L	L	L
Tamblyn 2015	H	H	H	H	L	L	L
Tierney 2005	H	H	H	H	L	L	L
Baker 2003	H	H	H	H	L	L	L
Feder 1995	H	H	H	H	L	H	L
Bachmann 2019	H	H	H	L	L	H	L
Baldacci 2012	H	H	H	H	L	H	L
Cleland 2007	H	H	H	H	L	L	L
Daniels 2005	H	H	H	H	L	H	L
Goeman 2009	H	H	H	H	L	L	L
Mold 2014	H	H	H	H	L	H	L
Veninga 1999	H	H	H	H	L	H	L
Blais 2008	H	H	H	H	L	H	L
Schneider 2008	H	H	H	H	L	L	L
Doherty 2006	H	H	H	H	L	H	L
Foster 2007	H	H	H	H	L	H	L
Harmsen 2010	U	H	H	H	H	L	L
Zeiger 1991	H	H	H	H	L	L	L

b.

Studies	Confounding bias	Selection bias	Classification bias	Intervention deviation bias	Attrition bias	Outcome measurement bias	Reporting bias	Overall
Coleman 2004	M	L	L	L	L	L	L	M
Dickinson 1998	S	S	L	L	L	L	M	S
Lindberg 2002	M	L	L	L	L	L	L	M
Yanchick 2000	S	L	L	L	L	L	L	S
Ruoff 2002	S	S	L	L	L	L	M	S
To 2008	S	S	L	L	L	L	L	S
Yawn 2008	S	L	L	L	L	L	M	S
Cho 2010	S	S	L	L	L	L	M	S
Kim 2015	S	L	L	L	L	L	M	S
Wright 2003	M	L	L	L	L	L	M	M
Ables 2002	S	L	L	L	S	L	L	S
Bender 2011	S	L	L	L	L	L	M	S
Cicutto 2014	S	L	L	L	L	L	M	S
Greene 2007	M	L	L	L	L	L	L	M
Jans 2000, Jans 2001	S	L	L	L	L	L	M	S
Licskai 2012	S	L	L	L	L	L	M	S
Mehring 2013	L	L	L	L	L	L	L	L
Mohammad 2019	S	S	L	L	L	L	M	S
Patel 2004	M	L	L	L	L	L	L	M
Roberts 2009	M	L	L	L	L	L	M	M
Rojanasarot 2019	M	L	L	L	L	L	M	M
Rojanasarot 2020	M	L	L	L	L	L	L	M
Andersen 2006	M	L	L	L	L	L	M	M
Abisheganaden 2001	M	L	L	L	L	L	L	M
Davies 2008	S	L	L	L	L	L	M	S
Gentile 2003	S	L	L	L	L	L	M	S
Goldberg 1998	S	L	L	L	L	L	M	S
Joe 1992	S	L	L	L	L	L	M	S
Lougheed 2009	S	L	L	L	L	L	M	S
Mackey 2007	S	L	L	L	L	L	M	S
McFadden 1995	S	S	L	L	L	L	M	C
Robinson 1996	S	L	L	L	L	L	L	S
Rowe 2008	S	L	L	L	L	L	M	S
Steurer-Stey 2005	S	S	L	L	L	L	M	S
Sukov 2000	M	L	L	L	L	L	L	M
Chew 2020	S	L	L	L	L	L	M	S

Kwok 2009	S	L	L	L	L	L	M	S
Pearson 1996	S	L	L	L	L	L	M	S
Akerman 1999	M	L	L	L	L	L	L	S
Chouaid 2004	S	L	L	L	L	L	M	S
Dalcin 2007	M	L	L	L	L	L	L	M
Doherty 2007	S	L	L	L	L	L	M	S
Edmond 1998	S	L	L	L	L	L	L	S
Pinnock 2003	S	L	L	L	L	L	M	S
Stell 1996	S	L	L	L	S	L	M	S
Abdulwadud 1999	S	L	L	L	L	L	M	S
Chou 2015	S	L	L	L	L	L	M	S
Eriskson 2005	S	L	L	L	L	L	L	S
Frieri 2002	S	L	L	L	L	L	M	S
Kanter 2002	S	L	L	L	L	L	L	S
Meng 1999	S	S	L	L	L	L	L	S
Morishima 2011	L	L	L	L	L	L	L	L
Schayck 1989	S	L	L	L	L	L	M	S
Tada 2015	S	L	L	L	L	L	L	S
Vollmer 1997	S	L	L	L	S	L	L	S
Wu 2001	S	L	L	L	L	L	L	S
Bell 1991	S	L	L	L	L	L	M	S
Pearson 1996	S	L	L	L	L	L	M	S
Pellicer 2001	L	L	L	L	L	L	L	L

Table e54. Interventions to improve guideline adherence for asthma assessment and maintenance management.

Study	Design, Size, Quality	Interventions	Clinical outcomes	Adherence outcomes
Additional patient specific input by specialised healthcare providers				
Armour 2007 Australia, 6 months follow-up	Cluster RCT, 50 pharmacies, 396 asthma patients. RoB: High (selection, performance, detection bias)	Intervention: Pharmacy Asthma Care Program (PACP), a community pharmacy-based asthma care model based on national guidelines. Pharmacists provided an ongoing cycle of assessment, management and review of pharmacy practice, in collaboration with general practitioners. Control: Usual pharmacists care.	- Higher proportion of patients improving from severe to non-severe asthma (OR: 2.68 [1.64, 4.37]). - Improvement in AQLQ (MD: -0.44 [-0.69, -0.18]), that did not reach MCID. - Lower daily dose of salbutamol (MD: -149.1mcg [-283.9, -14.14])	- Borderline improvement in BMQ scores (MD: -0.44 [-0.69, -0.18]). - Improved CQ scores (MD: 1.18 [0.73, 1.63]). - Higher proportion of participants with correct inhaler technique (48.6% more participants [39.2%, 58%]) and asthma action plan (40.4% [31.9%, 48.9%]), compared to baseline. - Higher proportion of patients adherent to preventer treatment (OR: 1.89 [1.08, 3.30]). - Higher proportion of participants using a combination of reliever and preventer medication (OR: 3.80 [1.40, 10.32]).
Coleman 2003 USA, 6 months follow-up	Comparative observational cohort, 645 asthma patients. RoB: Moderate (confounding)	Intervention: Patient specific letter (intervention packet describing specific issues identified in the management of the given patient) was sent to the patients' prescribers and pharmacists. The letter was accompanied by a laminated colour asthma education insert illustrating the national guidelines. Control: No intervention.	- Decrease in use of oral corticosteroids (suggestive of acute exacerbations) was more pronounced in the control group. (RR: 3.63 [1.73, 7.64]). - No significant impact on the number of ED visits(+), hospital visits(+) or number of hospital days(-).	- Increase in the proportion of patients receiving ICS (RR: 1.29 [0.97, 1.70], NS), LABA (RR: 3.78 [1.74, 8.22]), or at least one long-term control treatment (RR: 1.27 [0.96, 1.96]). - 46% of the participants in the intervention group, initially using high-dose SABA, were not using high-doses 6 months after the intervention. - No impact on the prescription of spacers (-) and peak flow meters (-)
Dickinson 1998 UK, 24 months (12 months before and 12 months after the intervention)	Before-After design, 1 centre, 100 participants. RoB: Serious (participants' and outcomes' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Nurse-run asthma clinic offering optimization of the inhaled therapies and inhaled devices; educational intervention to improve compliance. Control: Same patients, prior to the nurse clinic appointment		- Reduction in SABA use (MD: -1.2 [-0.5, -2.3]). - Increase in mean daily use of ICS (MD: 261 [146, 375.9]). - Improved treatment compliance (MD: 7.8% [1.34%, 14.26%]).

Herborg 2001 Denmark, 18 months (6 months baseline evaluation, 12 months post-intervention)	Cluster RCT, 31 pharmacies, 350 patients. RoB: High (selection, performance, detection bias)	Intervention: Therapeutic outcomes monitoring by a pharmacist, who identifies and resolves drug-related problems that might lead to therapeutic failure or adverse events. Control: No intervention.	- NS decrease in SABA use (25.7% decrease in the intervention vs 3.8% in the control group). - No between-group difference in the use of oral corticosteroids (-).	- Increase in the use of ICS (52.5% versus 9.1%, p=0.02) and LABA (163% increase vs 0.9% decrease, p=0.02) compared to control group. - NS decrease in the use of oral beta-2 agonists (42.2% decrease vs 1.2% increase) and theophylline (13.7% vs 7.1%), compared to the control group.
Lindberg 2002 Retrospective substudy Sweden, 2 years	Retrospective comparative cohort. 152 asthma patients. RoB: Moderate (confounding)	Intervention: Asthma nurse issuing prescriptions and/or written asthma action plans, providing information to patients and demonstrating inhalation technique. Control: No intervention.	- Lower number of ED visits in the intervention group (0.4 vs 1.1 visits)	- Higher proportion of patients who had a documented PEFR value (95% vs 71%), a PEFR diary (90% vs 19%), a spirometry performed (95% vs 60%), reversibility test (90% vs 43%), documented smoking history (90% vs 50%) and documented family history of asthma (90% vs 23%)
Lindberg 2002 Prospective substudy Sweden, 3 months	Cross-sectional patient survey. 267 asthma patients. RoB: Moderate (confounding)	Intervention: Asthma nurse practitioner (ANP) issuing prescriptions and/or written asthma action plans, providing information to patients and demonstrating inhalation technique. Control: No intervention.	- ANP group: Fewer reported at least 2 asthma attacks (6% vs 12%), night-time awakening due to asthma (26% vs 42%) or limitation in their physical activity (17% vs 28%), in the preceding week. - NS decrease in the use of SABA (57% vs 67%). - Similar EQ-5D scores.	- ANP group: Higher proportion of patients had a PEFR instrument (84% vs 50%), a written asthma action plan (66% vs 45%), received information about asthma prevention (89% vs 75%) and considered having adequate knowledge about their disease (91% vs 81%). - No difference in the proportion of patients receiving maintenance asthma therapy(+) or those who received inhalation device training(+).
Manfrin 2017 Italy, 9 months	Cluster RCT, 283 pharmacists, 1263 asthma patients RoB: High (selection, performance, detection bias)	Intervention: The Italian Medicines Use review (I-MUR). Structured face-to-face consultation with a pharmacist covering asthma symptoms, medicines used, attitudes towards medicines, adherence and identification of pharmaceutical care issues. Control: Delayed implementation of the intervention.	- Improved asthma control, measured using the Asthma Control Test (ACT, OR: 1.76 [1.33-2.33]).	- Decrease in the number of active ingredients administered to patients by 7% (p<0.01). - Improved treatment adherence by 40% at 6 months (p<0.01). - The intervention demonstrated cost-effectiveness
McLean 2003 Canada, 12 months	RCT 27 pharmacies, 631 asthma patients RoB: High (selection, performance, detection bias)	Intervention: Enhanced pharmaceutical care by an asthma trained and certified pharmacist. Control: Usual care.	- Symptom scores decreased by 50% compared to controlled. - PEFR increased by 11%. - Reduced days of work or school by 0.6 days/ month. - Reduced SABA use by 50%.	

			- 19% Improved QoL measured using the Juniper questionnaire. - 75% decrease in ED visits and in medical visits. - No difference in hospitalisations. - Decreased overall costs ($150 vs $351)	
Pilotto 2004 Australia, 9 months	Cluster RCT. 11 general practices, 170 asthma patients RoB: High (selection, performance, detection bias).	Interventions After presentation with an acute attack, trained respiratory nurses collected clinical data, reviewed patients and instructed them on inhaler technique, at presentation, two weeks and three months. General practitioners were reviewing the patients after every visit to the respiratory nurse. Control: Usual care delivered by GP.	- No difference in the mean change in quality of life (overall SGRQ and individual components) between groups. - No difference in pre- or post- bronchodilator FEV_1. - Patients in the intervention group were more likely to attend the outpatient department (8.5% vs 0%, p=0.009) but less likely to have work absences because of asthma (0% vs 7.8%, p=0.004).	
Premaratne 1999 UK, 3 years	Cluster RCT. 41 general practices, 3,621 patients surveyed at baseline and 1,613 at follow-up. RoB: High (selection, performance, detection, attrition bias)	Intervention: Intensive education of practice nurses, who in turn improved the management of patients and provided education. Control: No intervention.	- No difference in the number of patients experiencing night awakenings (3.9% from 4.0%), asthma attacks (0.6% from 0.5%), number of hospital admissions (0.91 versus 0.86%), or quality of life (+) even when correcting for confounding factors.	- Non-significant increase in the proportion of patients receiving any maintenance treatment and specifically those receiving ICS in the intervention, compared to the control group. - Non-significant increase in the rate of patients possessing a peak flow meter and those who have received an asthma action plan.
Wong 2017 Malaysia, 1 year.	Cluster RCT. 4 government health clinics, 157 asthma patients. RoB: High (selection, performance, detection, attrition bias)	Intervention: Introduction of a pharmacy management service to monitor asthma control (ACT), inhaler technique and medication adherence, using the Malaysian Medication Adherence Scale. Control: No intervention.	- Significantly higher proportion of patients achieving well-controlled asthma (90% vs 28.6%). - Significant improvement in asthma control test scores (p<0.001). - Reduction in the use of reliever medications (MD: -4.34 [-4.47, -2.74]).	- Significantly higher proportion of patients with correct inhaler's technique (change from baseline: 80.3% versus 15.6%). - Significantly higher medication adherence (92.5% versus 45.5%).
Yanchick 2000 USA, 2 years (1 year before, 1 year after)	Before-After study Primary care department of a hospital 300 asthma patients.	Intervention: Pharmacy department established a drug therapy monitoring clinic responsible for initiating and monitoring treatment plans,	- 88% decrease in ED visits and 92% decrease in hospital admissions for asthma exacerbations.	- Significant increase in the use of spacers (98% from 25%), peak-flow meters (88% from 12%) and asthma action plans (98% from 0%).

	RoB: Serious (confounding)	implementing clinical guidelines, providing educational programs, collecting and analysing outcome data. Control: Before	- Decreased SABA use (0.25 from 2.6 canisters of albuterol per month per person) - Increase in the proportion of controlled patients (95% from 11%).	- Increased proportion of patients received training on triggers avoidance (82% from 12%).
Zeiger 2014 USA, 1 year post-intervention ** both primary and secondary care.*	RCT 1,999 asthma patients RoB: High (performance & detection bias)	Patients using ≥7 SABA canisters in a year identified through pharmacy records. Intervention: Individualized recommendations were sent to patients and physicians. Control: Standard care, no intervention.	- Decreased SABA use (less patients used ≥7 canisters during follow-up, 50.7% vs 57.1%, p=0.007). - Unchanged asthma exacerbations, number of oral steroid courses, ED visits or hospitalizations.	- More visits to allergists (30.9% vs 16.8%) - Higher percentage of patients achieved ≥0.5 controller medication ratio (45.6% vs 37.4%, p<0.001)
Asthma care pathway				
Renzi 2006 Canada, 6 months	Cluster RCT, 104 primary care physicians, RoB: High (Attrition bias)	Intervention: Self-inking stamp checklist summarizing Canadian Clinical Practice Guidelines criteria for assessing asthmatic patients' control and therapy. Co-interventions: Group A: (i) CME event + (ii) encouragement to use the stamp + (iii) request to recruit 6 patients, where the stamp will be used. Group B: i + ii, Group C: I, Control: Guidelines were posted to the physicians (Group D).	- Decrease in patients with ER visits (7.8% vs 13.5%, P=0.009) and a trend over decreased hospitalizations (2.2% vs 4%, p=0.09)	
Ruoff 2002 USA, 6 months	Before-After study Private family practice group. 122 asthma patients. RoB: Serious (participants' and outcomes' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Flow sheets highlighting 14 clinical quality indicators were introduced in patient records, to be found by clinicians during next patient visit. Control: Before		- Higher proportion of patients receiving flow meter education (63.13% from 7.07%), inhaler technique education (78.95% from 7.07%), allergy skin testing (83.33% from 34.34%), yearly PFT (84.21% from 8.08%), vaccine prophylaxis (31.25% from 9.18%). - Increased documentation about nocturnal awakenings (94.74% from 4.04%), restricted physical activities (84.12% from 2.02%), hospitalizations (73.68% from 2.02%), ED visits (73.68% from 1.01%), frequency and timing of attacks (84.21% from 3.03%), days of

				school/work missed (73.68% from 1.01%), infections (83.33% from 21.21%). - Lower proportion of patients receiving smoking cessation advice (28.57% from 66.67%)
To 2008 Canada, 12 months	Before-After study 8 primary care practices, 1408 asthma patients. RoB: Serious (participants' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Primary Care Asthma Pilot Project involving an asthma care map, treatment flow chart, programme standards, a written asthma plan and, core elements of asthma education. Followed a participatory approach. Control: Before	- Reduction in self-reported asthma exacerbations (OR: 0.35 [0.28, 0.43], ED visits due to asthma (OR 0.47 [0.32, 0.62]), school absenteeism (OR: 0.37 [0.25, 0.54]), productivity loss (OR 0.49 [0.34, 0.71]), uncontrolled asthma symptoms, daytime (OR:0.34 [0.27, 0.42]) and night-time (OR: 0.29 [0.23, 0.37]).	- Increase in the proportion of patients receiving an asthma action plan (OR: 2.41 [1.88, 3.07]), using a PEFR (OR:3.39 [2.64, 4.35]) and those who had spirometry (19.82 [12.18, 32.27]). - Decreased number of participants had asthma education in the preceding (OR: 0.43 [0.35, 0.53])
Yawn 2008 US, 9 months	Before-After study 24 primary care practices. 194 physicians and 17 other clinicians, 1,691 people with asthma. RoB: Serious (outcomes' selection, confounding).	Intervention: The asthma APGAR tools including (i) a patient survey to collect information found on control scores, with the addition of patient reported information on asthma triggers, adherence and perceptions; and (ii) an asthma management algorithm. Control: Before		- Increase in the documentation of activity modification due to asthma (100% from 29-58%), daytime (81% from 62%) and night time (65% from 25%) symptom frequency, triggers (79% from 30%), treatment adherence (94% from 32%) and response (85% from 48%). - Increased prescription of anti-inflammatory medications (73% from 24%) - Increase in inhalers' technique testing (54% from 22%) and asthma education (54% from 8%) - Increase in the proportion of patients who had non-urgent asthma visit (21% from 4%)
Computer Decision Support Systems				
Cho 2010 Korea, 3 months ** Secondary care*	Before-after study, 377 physicians, 2,042 asthma patients, RoB: Serious (participants' selection, outcomes' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Easy asthma management programme; provides decision-making support for assessing asthma severity, choosing appropriate treatments and proper monitoring during follow-up. Training was offered on the use of the software and general training material. Control: Before.	- Significant improvement in diurnal and nocturnal symptom scores of asthma patients enrolled in the EAM pilot. - Significant improvement of the self-assessed asthma symptom improvement	- Significantly decreased prescription for oral beta-2 agonists (p=0.02), oral methylxanthines (p<0.001), and systemic corticosteroids (p<0.001) for maintenance treatment. - Significant increase in the prescription of inhaled corticosteroids combined with beta-2 agonsits.

Eccles 2002 UK, 24 months (intervention administration: at 12 months)	Cluster RCT, 60 practices, 2363 asthma patients RoB: High (selection, performance, detection, attrition bias)	Intervention: Computer decision support system prompting clinicians to follow guidelines, offering suggestions for management (including prescribing). Training workshop and materials. Control: Usual care	- No effect on SF-36, EQ-5D, the Newcastle asthma symptoms questionnaire, or the asthma quality of life questionnaire.	- No differences in the proportion of patients who the following assessments: lung function (OR: 0.94 [0.67, 1.33]), medication compliance (OR: 0.82 [0.58, 1.15]), asthma education and/or action plan (OR: 0.84 [0.4, 1.74]), smoking status (OR: 0.97 [0.65, 1.45]), or those who referred for smoking cessation advice (OR: 0.75 [0.45, 1.26]). - No difference in the proportion of patients who were prescribed on SABA (OR: 1.04 [0.83, 1.31]), ICS (OR: 0.95 [0.78, 1.16]), LABA (OR: 0.84 [0.59, 1.20]), oral steroids (OR: 1.0 [0.82, 1.22]) or oral bronchodilators (OR: 1.38 [0.56, 3.39]).
Kuilboer 2006 Netherlands, 10 months (5 months baseline, 5 intervention)	Cluster RCT, 32 general practices, 9798 asthmatic patients. Rob: High (selection, performance, detection, reporting bias)	Intervention: AsthmaCritic, a computer decision support system offering suggestions/ feedback regarding physicians' decisions. Control: No intervention.		- Modestly increased number of planned asthma visits, peak-flow measurements, which however did not reach statistical significance in people of a higher age. - No difference in FEV_1 measurements among adult patients. - Decreased prescription of cromoglycate in younger ages.
Martens 2007 Netherlands	Cluster RCT, 53 GPs (14 practices), 89,358 patients with various presentations. Asthma numbers were not specified. RoB: High (selection, performance, detection, reporting bias)	Intervention: Computer reminder system containing reminders regarding alternative drug types, doses, administration routes, indications, duration of prescribing, non-pharmacological options. Control: No asthma intervention.		- Increased prescription of maintenance treatment for mildly persistent asthma (44% versus 27%). Increased use of ICS among all asthma patients (33% vs 25%). No difference in the prescription of SABA or SAMA.
McCowan 2001 UK, 6 months	Cluster RCT, 19 practices, 477 patients RoB: High (selection, performance, detection bias)	Intervention: Computer decision support system prompting clinicians to offer appropriate care (including prescribing). Control: Usual care.	- Decrease in patient-initiated consultations (OR: 0.59 [0.37, 0.95]); no impact on the number of practice initiated reviews (OR: 0.69 [0.21, 2.21]), hospital admissions (OR: 0 [0, 3.44]), ED presentations (OR:0 [0, 9.16]) or outpatient visits (OR: 0.64 [0.09, 3.38]). - Decrease in the number of exacerbations (OR: 0.43 [0.21, 0.85]) and the use of emergency nebulisations (OR: 0.13 [0.01,	- No impact on the proportion receiving a flow meter (OR: 1.52 [0.58, 4.01]), or a self-management plan (OR: 1.32 [0.42, 4.16]).

			0.91]), without any impact on the use of oral corticosteroid (OR: 0.42 [0.14, 1.29])	
Tamblyn 2015 Canada, up to 33 months	Cluster RCT, 81 GPs, 4,447 asthma patients. RoB: High (selection, performance, detection bias)	Interventions: ADS system using Canadian consensus guidelines to address problems in asthma management: recognition of poor asthma control; underutilization of prophylactic therapy lack of asthma action plan, insufficient patient education and support for self-monitoring. Training offered. Control: Standard care, which included electronic patient records.	- Non-significant decrease in the rate of out-of-control asthma rate (46.2 vs 54.7 per 100 patients per year, -8.7 [-24.7,7.3]. - Significant decrease among those with out-of-control asthma at presentation (-28.4 [-55.6,-1.2])	- Significant increase in the ratio of doses of inhaled corticosteroid use to fast-acting beta-2 agonists in the intervention group (difference 0.27 [0.02-0.51]).
Tierney 2005 USA, 3 years (2 years baseline, 1 intervention)	2x2 factorial RCT, 246 physicians (internists) & 20 outpatient pharmacists, 706 patients. RoB: High (selection, performance, detection bias)	Intervention: Computer generated encounter form listing medications and care suggestions. It also included a list of all medications for which the patient was eligible. These were given to intervention clinicians & pharmacists. Control: no intervention	- No impact on quality of life measured with SF-36, or symptoms, measured with AQLQ. - No impact on the number of ED visits or hospitalisations for any cause, or for airway diseases exacerbations.	- No differences in adherence to care suggestions. • Authors commented this may have been an underpowered study.
Guideline introduction (local or national)				
Baker 2003 UK, 2 years (1 year baseline, 1 year post-intervention)	Cluster RCT, 81 general practices, 2,679 asthma patients RoB: High (selection, performance, detection bias)	Intervention: Guidelines dissemination, prioritized review criteria, (i) with or (ii) without feedback. Control: Guidelines dissemination alone.	- Small increase in asthma symptom scores compared to control, that did not exceed MCID (p=0.02)	- No difference in the documentation of diagnostic criteria used (+), the use of PFR diurnal variation or variability for confirming equivocal diagnosis (-). - No difference in LABA prescription rate (-), evaluation of adherence (-), evaluation of SABA requirements (-), smoking cessation advice (+). - No difference in patients satisfaction with clinical care (-) or the information received (-).

Feder 1995 UK, 1 year.	Cluster RCT, 24 general practices, 240 asthma patients RoB: High (selection, performance, detection, reporting bias)	Intervention: Introduction of local guidelines with local educational interventions and a stamp checklist. Control: No intervention.		- Increase in the proportion of patients who had their inhaler technique checked (RD: 12.9 [1.9, 23.9]). - No impact on peak flow documentation (RD 0.7 [-15.2, 16.2]), symptoms review [RD: 1.0 [-13.8, 15.9]), evaluation of occupation (RD: 12.6 [-4.9, 30.2]), smoking evaluation RD:5.6 [-17.2, 28.3]). **Subgroup where the stamp was used:** Significant improvement in all parameters: peak flow evaluation (OD: 27.3 [8.1, 92.1]), inhaler technique (OR: 41.6 [17.1, 100.9]), Symptoms review (OR: 44.9 [6.1, 333.5]), Occupation (OR: 15.3 [6.9, 34.0]), smoking evaluation (OR: 66.7 [9.0, 465.8])
Kim 2015 Korea, 8 years.	Retrospective health insurance claims database review, Before-After design. 235,755 asthma patients. RoB: Serious (outcomes' selection, confounding).	Intervention: Introduction of the "Korean Asthma Management Guideline 2007". Control: Before.		- Significant increase in the ICS prescription rate (16.4% vs 13.3%, p<0.001). However, the overall trend of ICS prescription rate, estimated using the trend before guideline dissemination, did not change. Subgroup analyses according to the health setting revealed that the dissemination of the guideline led to modest increase in ICS use in secondary (OR: 1.15 [1.02, 1.30]) and general hospitals (OR: 1.10 [1.04, 1.16]), but not in primary care (OR: 0.98 [0.94, 1.02]), here most patients were reviewed
Wright 2003 UK, up to 5 years baseline (retrospective), and up to 10 months post-intervention	Prospective, comparative cohort. 180 general practices, 1453 asthma patients. RoB: Moderate (outcomes' selection, confounding)	Intervention: National, evidence-based guideline implementation including developmental interventions (to obtain commitment and adapt to a local summarized guideline and agree on implementations strategy), dissemination (education meetings and educational outreach visits) and reinforcement. Control: Passive dissemination of the guideline.		- Non-significant decrease in the proportion of clinicians reporting smoking status (MD:-7 [-14,0]) - Non-significant increase in the proportion of patients receiving inhaler technique training (MD:2 [-2, 6]) - Significant increase in the prescriptions of bronchodilators and ICS, perhaps due to seasonal effects. - Higher proportion of clinicians in the control group had seen the guideline (75% vs 25%).
Medical education				
Ables 2002	Before-after study. 1 Family Care Center,	Intervention: Three compulsory lectures on (i) electronic patient	- Decrease in the number of ED visits (from 3 to 0) and hospitalizations (from 2 to 0),	- Significant increase in the documentation of asthma severity classification from 25 to 51% (p <0.001).

US, 1.5 years (baseline, intervention, post-intervention, 6 months each).	301 asthma patients and/or AR. RoB: Serious (confounding, missing data).	records, (ii) asthma severity and classification and (iii) inhaler's technique; additional instructions for attending physicians; pocket cards; reminders in patient notes. Control: Before.	although not all events may have been successfully tracked.	
Bachmann 2019 US, 3 years (baseline, intervention, post-intervention, 1 year each).	Cluster RCT. 49 general practices, 5070 asthma patients. RoB: Serious (selection, performance, reporting bias	Intervention: Training in the use of Practical Approach to Care Kit (PACK) guide, a decision support tool. Initial and maintenance training including short interactive group sessions (90'), weekly or fortnightly. Control: PACK guide without trianing		- Borderline increased likelihood of starting or changing treatments (19% vs 15.1%, p = 0.012) and of having a spirometry requested (11% vs 8.1%, p = 0.012). - Increased asthma scores (reflecting the treatment step patients are offered and whether they had spirometry). However, significance was lost in adjusted analyses. - No improvement in the assessment of comorbidities and smoking cessation practices.
Baldacci 2012 Italy, 1 year.	Cluster RCT. 107 GPs, 1820 asthma patients. RoB: High (selection, performance, detection, reporting bias).	Intervention: Single course on ARIA and GINA guidelines, patient and caregiver education. Immunotherapy, prescriptions appropriateness and pharmacoeconomy. Control: No intervention.		- No significant between group difference in the adherence to GINA guidelines.
Bender 2011 US, 3 years (2 intervention, 1 pot-intervention).	Before-after study. 57 primary care practices, 15,508 asthma patients RoB: Serious (outcomes' selection, confounding	Intervention: 3 half-day in-practice coaching visits focusing on asthma diagnosis, management, guidelines, pathogenesis, effective communication, case studies, case discussion. Practices also received spirometers and patient toolkits. Control: Before		- Higher proportion of patients received inhaled corticosteroids (50% from 25%). - Significant increase in the proportion of patients with an asthma action plan (20% from 0%). - Significant increase in the proportion of patients who had spirometry at least once (40% from 0%).
Bender 2015 US, 2 years.	Before-after study. 13 primary care clinics, 2,392 asthma patients. RoB: Serious (outcomes' selection, confounding).	Intervention: A full-day training followed by 2 in clinic follow-up visits, spirometry demonstration and practice every year. Introduction of care and action plan templates in the electronic patient records. Online toolkit with access to manuals, patient materials, videos on spirometry and		- Significant increase in the documentation of spirometry from 6.7% to 42.5%, guideline-based severity assessment from 12.8% to 29.4%, asthma action plan administration from 1.8% to 7.6%, and prescription of ICS from 33.1% to 41.6%. However, more than half of asthma patients did not receive this 4 elements.

		patient communication, FAQs and links to other web resources. Control: Before.		
Cicutto 2014 US, 18 months post-intervention	Before-after study. 2 hospital outpatient centres and 1 community health centre, 767 asthma patients. RoB: Serious (outcomes' selection, confounding).	Interventions: Multidisciplinary, interactive workshops, asthma champion workshop for local clinic site leaders, coaching visits in clinics, clinician support tools, patient education materials and teaching aids, resource websites, provider practice feedback reports. Control: Before		- Significant improvements in all domains assessed: at least one spirometry documented (14% from 3%), documentation of asthma control (any control indicator 67% from 59%; complete assessment: 20% from 1%), reliever inhaler prescription (94% from 55%), controller medicine prescription (71% from 39%), inhaler technique demonstration (18% from 1%), asthma action plan (29% from 2%), follow-up visit arrangement (37% from 20%). - Prespecified targets were only met for the prescription of reliever medication and inhaler technique demonstration.
Cleland 2007 UK, 6 months	Cluster RCT. 13 general practices, 629 asthma patients. RoB: High (selection, performance, detection bias)	Intervention: 3-hour interactive seminar using active learning techniques. Included brief lectures, effective communication training, case studies, role play and patient resources. Control: No intervention.	- Statistically significant improvement in the mini-AQLQ, that did not exceed the MCID. - No difference in the ACQ, SABA use or number of oral steroid courses.	
Daniels 2005 USA, unclear duration.	Cluster RCT. 16 community health centres, 400 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Two half-day training sessions using principles of active adult learning focusing on the definition, classification, treatment, and prevention of asthma. Tools to support practice-level change (templates and flowcharts). Finally, resources, including asthma kits with peak flow meters, spacers and educational material. Control: No intervention.		- Statistically significant increase in the use of peak flow in the clinic (+39% vs +0.7%, p=0.008) and in the documentation of interval symptom history (+11% bs +0.04%, p=0.006), compared to the control group. - Trend over increased documentation of the family smoking history (+18% vs +10%, NS), discussion of environmental factors (+10% vs +0.7%, NS), reinforcement of maintenance and rescue plans (+19 vs +3%, NS), prescription of inhaled anti-inflammatory (+19% vs +9%, NS), and scheduling follow-up visit (+28% vs +11%)
Goeman 2009 Australia, 4 months	Cluster RCT. 42 GPs, 107 asthma patients.	Intervention: 2-hour session, participation in videorecorded simulated patient consultation, 1-hour academic detailing visit at GPs usual	- No significant changes in patients' outcomes (asthma symptom control, quality of life, lung function, treatment adherence, or asthma knowledge.	- Non-significant increase in asthma plan ownership (29% vs 15%).

	RoB: High (selection, performance, detection bias)	practice location for individually tailored training/ Control: Information packs, and a simulated patient consultation		
Greene 2007 USA, 2 years (1 year baseline data, 1 year post-intervention) * Secondary care	Before-after study. 118 residents, 441 asthma patients. RoB: Moderate (confounding).	Intervention: 12 one-hour didactic sessions using chronic care model to teach system-based practice and practice-based learning and improvement. Intensive chart reviews and quality improvement projects to promote understanding of the evidence and sharpen skills in analysing and solving problems. Control: No intervention.	- Significant decrease in the ED visits for asthma (-43.8% vs -2.9%) and for any cause (-28.7% vs +2.0%). - Significant cost benefit (36% decrease in costs in the intervention arm).	
Mold 2014 USA, 6 months **Local learning collaboratives evaluated as educational intervention here*	Cluster RCT. 43 general practices, 1,016 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Monthly-one hour sessions for practice facilitation (PF) with or without local learning collaboratives (LLC), in addition to control intervention. Control: Performance feedback, academic detailing, asthma guidelines and a toolkit with the ACT, asthma APGAR and asthma action plans.		- PF+LLC, LLC, PF and control, led to statistically significant improvement in 5, 4, 3 and 2 out of six guideline implementation indicators compared to baseline. - In multivariate modelling, PF was associated with a significantly improved assessment of asthma severity (OR: 2.5 [1.7-3.8]) and assessment of the level of asthma control (OR: 2.3 [1.5-3.5]), while LLC was not superior to control for any indicator.
Veninga 1999 Netherlands, Norway, Sweden, Slovakia, 12 months.	Cluster RCT. 665 GPs. RoB: High (selection, performance, detection, reporting bias)	Intervention: Two educational meetings. Self-learning based on individual auditing and feedback of performance for small peer groups. Control: Educational intervention about a different disease (not asthma).		- No significant changes in the proportion of patients receiving ICS, continuous bronchodilator therapy, receiving adequate ICS dose, or the proportion of patients receiving oral corticosteroids
Quality improvement process				
Blais 2008 Canada, 33 months (12 baseline, 9 intervention, 12	2 RCTs, one with 71 physicians and one with 57 pharmacists. RoB: High (selection, performance, detection, reporting bias)	Intervention: Audit and 3 consecutive letters providing feedback on participants practice (compliance with five appropriate-use criteria). Control: No intervention		- No differences were observed, as the rates of timely SABA renewal, LABA and LABA/ICS prescriptions were similar between groups.

post-intervention)				
Jans 2000, Jans 2001 Netherlands, 1 year	Before-after study. 14 general practices, 370 asthma patients. RoB: Serious (outcomes' selection, confounding).	Intervention: Identification of barriers, training on lung function, pharmacotherapy, inhalation techniques, ways to improve appointment system and referrals. Frank discussion of controversial aspects of the guidelines. Practice feedback and peer review. Control: no intervention & before.	- Statistically but not clinically significant improvement in morning PEFR (between group difference: 2.3 [0.3-4.2]) and deterioration in emotional reactions score (difference: -3.4 (-6.7, -0.1). No changes in other indicators.	- Significant increase in the percentage of patients with two or more consultations per year to monitor symptoms (82% vs ~20%). - Significant increase in the proportion of patients with at least one PEFR measurement (84% vs ~ 20%). - Significant increase in monitoring of medication compliance (60% vs 50%) and inhalation technique (42% vs 21%). - More persons quitted smoking or were advise to do so in the intervention group (84% vs 59%). - No significant between-group difference in the prescription of anti-inflammatory agents, influenza vaccination, or FEV_1 measurement.
Licskai 2012 Canada, 2 years.	Before-after study. 33 GPs, 519 asthma patients. RoB: Serious (outcomes' selection, confounding). ** Same patients evaluated at baseline and during follow-up.	Intervention: Patient, practice, and health system level targeting. Problem identification, education, identification of barriers and select, tailor, implement interventions for change. Control: Before.	- Significant decrease in patients with at least one or more symptoms beyond acceptable limits (36% from 67%). This was maintained on long-term follow-up (22 months). - Sigificant decrease in urgent healthcare utilization visits (1.45±2.91 visits/year, from 2.94±4.36).	- Despite of a good baseline implementation of the six guideline-based care objectives, there was an increase in the proportion of patients prescribed controller therapy (95% versus 86%) and after the intervention, 98% of those requiring controller therapy, were prescribed.
Mehring 2013 Germany, 5 years	Longitudinal evaluation Primary care in Bavaria, 109,042 asthma patients. RoB: Low	Intervention: German Disease Management Programs include quality improvement measures with half-yearly feedback reports and benchmarking, introduction of standards, medical education, introduction of reminder systems and financial incentives to patients. Control: Before	- Significant decrease in hospital admissions (0.7% from 2.8%). - Significant increase in the proportion of patients with less than weekly or no symptoms at all (69.8% from 59.3%).	- Steady increase in the number of patients included in the DMP program (109k pts in 2010, from 21k in 2006). - Decrease in the prescription of oral corticosteroids (5.9% from 15.7%). Small decrease in SABA use, with parallel increase in the use of LABA. - Significant increase in the proportion of patients with an asthma action plan (69.3% from 40.3%) and those receiving self-management education (23.4% from 4.4%).
Mohammad 2019 Syria,	Before-after study	Intervention: Audit form to assess initial prescription of ICS/LABA by residents. Filled forms were reviewed		- Increase in the proportion of patients treated in line with guidelines (80% from 15.6%, p=0.002)

* Secondary care	1 Hospital (internal medicine department), 90 patients RoB: Serious (participants' and outcomes' selection, confounding).	by a trainer respiratory physician for compliance. In case of discrepancies, on-site training was provided. Control: Before.		- Increase in the proportion of patients receiving education for treatment avoidance (95.6% from 64.4%, p = 0.004). - All audited patients received inhaler technique training and an asthma self-management plan both before and after the intervention.
Mold 2014 USA, 6 months **Practice facilitation is evaluated as a quality improvement process here*	Cluster RCT. 43 general practices, 1,016 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Monthly-one hour sessions for practice facilitation (PF) with or without local learning collaboratives (LLC), in addition to control intervention. Control: Performance feedback, academic detailing, asthma guidelines and a toolkit with the ACT, asthma APGAR and asthma action plans.		- PF+LLC, LLC, PF and control, led to statistically significant improvement in 5, 4, 3 and 2 out of six guideline implementation indicators compared to baseline. - In multivariate modelling, PF was associated with a significantly improved assessment of asthma severity (OR: 2.5 [1.7-3.8]) and assessment of the level of asthma control (OR: 2.3 [1.5-3.5]), while LLC was not superior to control for any indicator.
Patel 2004 US, 1.5 years (6 months baseline and 1 year post-intervention)	Before-after study. 16 general practices, 6,486 asthma patients. RoB: Moderate (confounding).	Intervention: Identification of barriers and obstacles, education and implementation of best practices identified through literature review and participation in a citywide asthma advocacy organisation. Control: Before	- Decreased ED visits (88/1000 patients, from 148/1000) - Decreased hospital admissions related to asthma (37/1000 patients from 81/1000).	- Significantly improved documentation for asthma diagnosis (98.6% from 83.3%) and for patient education (26.1%, from 15.7%). - No improvement in documentation of peak flow ownership/use, smoking cessation advice, or influenza vaccination
Roberts 2009 US, 2 years	Before-after study. 1 Academic pulmonary division, 650 asthma patients. RoB: Moderate (outcomes' selection and confounding).	Intervention: Education, selection of performance indicators, auditing, quarterly confidential clinician performance feedback scorecards. Control: Before		- Significantly improved adherence to asthma management guidelines (98% from 76-92%). - Significantly increased proportion of patients prescribed ICS (96% from 83.5%).
Rojanasarot 2019 USA, 1.5 years (1 year intervention, 6	Before-after study. 65 community health centres, 4,393 asthmatic patients. RoB: Moderate	Intervention: Enhancing care of patients with asthma quality improvement process. The process included improvement activities using the Plan-Do-Study-Act (PDSA) cycle		- Significantly increased documentation of the following domains: Asthma severity (RR 1.44 [1.33-1.56]), asthma control test (3.85 [3.41-4.36]), pulmonary function testing (1.95 [1.62-2.34]), asthma education (RR 2.21 [1.99-2.45]), asthma action plan (RR 2.32 [2.03-2.65]), controller

months post intervention)	(outcomes' selection and confounding).	and learning collaboratives with other centres. Control: Before.		medication prescription (RR 1.97 [1.516-2.57]). These changes persisted six months after the intervention.
Rojanasarot 2020 USA, 3 years (1 year baseline, 1 year intervention, 5 months post-intervention)	Interrupted time series. 15 health centres in 4 States, 1,828 asthma patients. RoB: Moderate (confounding)	Intervention: Quality improvement based on Plan-Do-Study-Act cycles to carry out changes that led to asthma guidelines adoption. Control: Before	- Significant decrease in the average number of ER visits and hospitalizations due to asthma from 2.22 to 1.38 and from 1.97 to 1.04 per 100 patients, per month, respectively. Post intervention, the respective rates were 1.02 and 1.09 per 100 patients per month.	
Schneider 2008 Germany, 1 year	Cluster RCT. 96 GPs, 256 asthma patients. RoB: High (selection, performance, detection bias)	Intervention: Quality improvement circles with auditing and benchmarking, where GPs receive individual feedback and the names of the best performing GPs, who would then explain how best practice was achieved. Control: Traditional quality improvement, without benchmarking.	- Non-significant trend towards decreased frequency of unscheduled ED visits.	- Non-significant trend towards improved guideline adherence in drug treatment. - Significant increase in the delivery of individual emergency plans in both arms, however the overall use remained low, at 10-15% of patients. - No change in asthma education, peak flow meter at home and use of asthma diary. - No difference between the interventions.
Participation in a clinical trial				
Andersen 2006 Denmark, 3 years (1 year baseline, 1 intervention, 1 post-intervention)	Observational cohort study. 175 general practices, 65,013 asthma patients. RoB: Moderate (outcomes' selection, confounding)	Intervention: Participation in an RCT evaluating the asthma management (comparing to different doses of Symbircort). Control: No intervention.		- Significantly improved prescription patterns were observed in both groups. However, no difference between groups was observed in the use of either non-fixed or fixed ICS and inhaled beta-2 agonist, or on the use of the trial sponsor's drug.

*AQLQ: Asthma-related quality of life questionnaire, BMQ: Brief Medication Questionnaire, CQ: Consumer asthma knowledge questionnaire, ED: Emergency Department, MCID: Minimal clinically important difference.

Table e65 Interventions to improve guideline adherence for acute asthma attacks assessment and management.

Study	Design, Size, Quality	Interventions	Clinical outcomes	Adherence outcomes
Acute asthma care protocol/pathway				
Abisheganaden 2001 Singapore, 9 months	Before-after study. Community-based teaching hospital, 183 asthma patients RoB: Moderate (confounding)	Intervention: Introduction of an asthma care pathway. Control: Before.	- No significant change in length of stay. - No significant change in asthma relapse after discharge.	- No change in the use of PEFR monitoring, or the use of systemic corticosteroids. - Decrease in the use of antibiotics (30.4% from 62.7%) and request of sputum tests (18.6% from 34.3%). - Increase in the proportion of patients who had their salbutamol (73.7% from 49.3%) and oxygen (73.8% from 25.8%) reviewed.
Davies 2008 Canada, 1 year (3 months baseline, 6 months intervention, 3 months post-intervention).	Before-after study. Community hospital, 128 asthma patients. RoB: Serious (outcomes' selection and confounding)	Intervention: Clinical pathway introduction, medical education including 2x2-hour core sessions, pre-learning package and supportive information. Local champions appointed as mentors and advocates. Control: Before		- SABA use was assessed in a higher proportion of patients (72.9% from 52.5%, p=0.026). - Higher proportion of patients received an asthma action plan (23.9% from 3.8%, p = 0.001), and asthma education (27.1% from 3.8%, p < 0.001).
Gentile 2003 USA, 14 months (2 baseline, 12 post-intervention)	Before-after study. ED of a tertiary hospital, 481 asthma patients. RoB: Serious (outcomes' selection and confounding).	Intervention: Introduction of an acute asthma protocol with specific criteria for diagnostic testing, aiming to safely reduce unneeded tests (chest x-rays and arterial blood gases). Control: Before.	- Unchanged hospital admission rate (19% from 20%) or hospital length of stay (3.12±1.6 from 3.83±2.8, p=0.26).	- 55% reduction in the number of chest radiographs (from 40% to 18%, p<0.001) - 57% reduction in the number of arterial blood gases (from 9.4% to 3.5%).
Goldberg 1998 USA, 25 months (6 baseline, 7 months interval, 9 post-intervention).	Before-after study. 1 ED, 246 asthma patients. RoB: Serious (outcomes' selection and confounding).	Intervention: Introduction of a critical pathway protocol for acute asthma assessment and management. Control: Before.	- No between group difference in the rate of hospitalizations or the number of endotracheal intubations.	- Decline in the use of oxygen by 19% (p=0.001), handheld nebulizer treatments by 33% (p=0.001), intravenous steroids by 13% (p=0.034) and saline locks by 15% (p=0.011). - Increase in the use of metered-dose inhalers with spacer by 64% (p=0.001) and oral steroids by 18% (p=0.027).

				- Non-significant trends over decreased ABG testing by 4% and lower length of ED stay (9%).
Joe 1992 USA, 14 months (3 baseline, 2 post intervention and 3 late follow-up, with intervals between them)	Before-after study. 1 ED, 350 asthma patients. RoB: Serious (outcomes selection and confounding).	Intervention: Introduction of an asthma care protocol, which was posted in the ED. Training included a 10-minute verbal presentation and three page summary of the literature. Control: Before		- No changes in treatment patterns were consistent both in short and later follow-up intervals
Lougheed 2009 Canada, 5 months.	Comparative cohort with concurrent and historical control. 10 EDs, 1262 asthma patients. RoB: Serious (outcomes' selection and confounding).	Intervention: Asthma care pathway including instructions, pre-printed physicians' orders, patient asthma action plan, a wall poster, and a pocket card. Implemented through peer-facilitated case-base workshops. Centres were encouraged to appoint champions. Control: No intervention/ Before		- Pathway use varied between 6-60% across centres. - Significant increase in ABG evaluation, use of bronchodilators by MDI, use of ICS and the use of oxygen, compared to control. Trend over increased use of systemic steroids. - Significantly increased reporting of PEFR, systemic steroids use and respiratory therapist's involvement in the care of patients when using the pathway. - No between group difference in the time to first bronchodilator and systemic steroid administration. - Significant decrease in PEFR documentation both in intervention and control centres.
Mackey 2007 Canada, 10 months (5 baseline, 5 post-intervention)	Before-after study. 1 ED, 141 asthma patients. RoB: Serious (outcomes' selection and confounding).	Intervention: A 4-page asthma care map for documenting history, PEFR medications, treatment, discharge instructions and nursing notes. Implementation through medical education and feedback to the ED staff. Control: Before.	- No significant differences in patients' outcomes within 48 hours. - There was a trend toward earlier relapses [within 48 hours] in the pre-intervention group (p=0.23)	- No change in the ED length of stay (2h25mins from 2h14mins). - Increase in the use of SABA during the first hour (median 3 vs 2, p=0.001) and during ED stay (median 4 vs 2, p=0.003). Increase in the use of SAMA during ED stay (medium 2 vs 1, p=0.0001). - No significant change in the prescription of discharge medications (ICS, OCS, prednisolone).
McFadden 1995 USA, 32 months (8 baseline, 24 post-intervention)	Before-after study. 1 ED, 1,513 asthma patients. RoB: Critical (participants' and outcomes' selection and confounding)	Intervention: Introduction of an asthma care pathway. Control: Patients treated without the protocol before or after the intervention period.	- Decrease in the number of hospital admissions by 27% and of ICU admissions by 41%. - Decrease in the frequency of return visits within 24 hours by 66%.	- Suboptimal use of PEFR for informing the decision for hospital admission or discharge. - The average time in the ED decreased by 50 minutes during the intervention period (p<0.001), but then rose again by an average of 16 minutes when protocol adherence diminished. In addition, the proportion of patients who stayed in ED for at least 3 hours decreased

			** During the last 12 months of the intervention, use of the pathway decreased and patients outcomes deteriorated.	(15% from 34%) during the intervention, but then increased to 47% again.
Robinson 1996 UK, 1 year (6 months baseline, 6 post-intervention)	Before-after study. 1 ED, 175 asthma patients. RoB: Serious (confounding)	Intervention: Introduction of a pre-printed, structured form for the assessment and management of acute asthma, following national guidelines and including prompts for demographic details, current symptoms, past medical history, physical examination, management, follow-up arrangements and discharge medications, according to severity. Control: Before.	- No significant differences in the admission rates (46% from 50%), or the rates of ED reattendance (0% from 3%)	- Significantly improved documentation of past asthma history (93% from 69%), usual medications (95% from 81%), respiratory rate (95% from 81%), predicted PEFR (75% from 23%), and percentage of predicted PEFR (62% from 1%). Significant decrease in the documentation of pulse rate (89% from 100%) and chest examination findings (91% from 100%). - Increased proportion of patients were treated in line with guidelines (89% from 50%) and had their inhaler technique checked (44% from 3%). - Less inappropriate discharges (28% from 54%). - No difference in the discharge prescriptions and follow-up plans.
Rowe 2008 Canada, 30 months (15 baseline, 15 post-intervention, 2 follow-up audits)	Before-after study. 1 ED, 387 patients. RoB: Serious (outcomes' selection and confounding)	Intervention: 4-page ACM developed by a multi-disciplinary team using evidence-based methods. Documentation of history, medications, physical findings, treatment, discharge instructions, PEFR, nursing notes. Control: Before.	- No impact in the proportion of patients admitted to the hospital (from 9% to 13% and 5%).	- Increasing use of oral steroids (75% and 68% versus 57% before, p<0.001, OR: 1.6 [1.0-2.7]) and earlier administration (<60 mins, p<0.01). - Decreasing use of supplemental oxygen (from 24% pre-intervention, to 21% and later 7%). - No change in the prescription patterns and timings of SABA and SAMA. - Increased time of ED stay from 181 pre-intervention to 209 and 265 mins, p <0.001). - Significant increase in oral steroids prescription at discharge (66% and 69% from 55%) and progressive decrease in the proportion discharged without any steroids (21% and 14% from 32%). Increased proportion discharged on ICS (OR: 3.4 [1.5-7.6]). - Care pathway was utilized in 67-70% of patients.
Steurer-Stey 2005 Switzerland, 6 years (19 months baseline, 3.5 years interval, 7	Before-after study. 1 urban ED, 311 asthma patients. RoB: Serious	Intervention: Asthma care pathway and local guideline. Training offered locally to the department. Control: Before		- Significantly increased respiratory rate reporting (65% from 14%), assessment of airway obstruction (96% from 53%), of pulse oximetry (84% from 24%). - Decreased frequency of ABGs (6% from 16%).

months post-intervention).	(participants' and outcomes' selection and confounding). ** Very long interval between the baseline and post-intervention measurements.			- Significant increase in the administration of systemic steroids (68% from 43%) in the ED and as discharge medications (70% from 37%); SABA upon arrival in the ER (96% from 88%), and in repeated SABA administration (84% from 31%). - Significant increase in PEFR use for evaluating treatment response (85% from 36%), in inhalers' technique documentation (14% from 5%).
Sukov 2000 USA, 3 months (1 baseline, 2 post-intervention)	Before-after study. 1 ED, 447 asthma patients. RoB: Moderate (confounding)	Intervention: 3-page care pathway developed through a modified- Delphi approach. Implemented after an educational session for all ED staff. Control: Before	- No significant improvement in the proportions of patients admitted to the hospital or the relapse rate.	- Significantly increased proportion of patients receiving 3 SABA doses within 90 minutes (86% from 63%). Significant decrease in ED length of stay (3.39±1.88 hours from 3.84±2.12 hours). - Trend towards increased use of PEFR on arrival (73% from 62%). - Care pathway was only utilized in 55% of patients in the intervention group.
Additional patient specific input by a specialized health professional				
Chew 2020 Singapore, 17 months.	Comparative observational study. 1 ED, 637 asthma patients. RoB: Serious (outcomes' selection and confounding)	Intervention: Afterhours respiratory nurse reviewed patients attending with acute asthma, offering a brief educational intervention, clinical decision support to emergency department physicians and audited clinical care. Control: Routine care without input by a respiratory nurse.		- Higher compliance with oral corticosteroids prescription, but not ICS prescription, in the intervention group. - More patients referred for follow-up review in the intervention group. - Low referral rate to the respiratory nurse by ED physicians.
Computer Decision Support Systems				
Kwok 2009 Australia, 14 months (7 baseline, 7 post intervention, with interval)	Before-after study. 1 ED, 100 patients. RoB: Serious (outcomes' selection and confounding).	Intervention: The Asthma Clinical Assessment Form and Electronic Decision Support (ACAFE), an online point of care clinical decision support system. Based on national asthma guidelines. Control: Before		- Significantly higher rates of documentation of asthma severity (98% from 18%), intensive care unit admission (90% from 14%), smoking history (98% from 64%), and asthma precipitants (94% from 66%). - Significantly higher rates of asthma management plan documentation (76% from 16%, $p<0.01$). - Trends over increased documentation of pulmonary function, smoking cessation advice and oral corticosteroids discharge prescription.

Introduction of a local or national guideline				
Pearson 1996 UK, 2 years (1 year baseline, 1 year post-intervention).	Audit. 36 teaching and district hospitals, 1,666 asthma patients. RoB: Serious (outcomes' selection and confounding)	Intervention: Introduction of a national asthma guideline. Control: Before		- Increase in the frequency that respiratory physicians administer a self-management plan (20% from 12%). No similar results in the non-specialists. No difference in the other seven standards that were assessed.
Medical education				
Veninga 1999 Netherlands, Norway, Sweden, Slovakia, 12 months.	Cluster RCT. 665 GPs. RoB: High (selection, performance, detection, reporting bias)	Intervention: Two educational meetings. Self-learning based on individual auditing and feedback of performance for small peer groups. Control: Educational intervention about a different disease (not asthma).		- No significant change in the proportion of patients receiving oral corticosteroids
Quality improvement process				
Akerman 1999 USA, 3.5 years (1 year baseline, 2.5 years intervention)	Comparative cohort with concurrent and historical control. Inner-city ED, 300 asthma patients. RoB: Moderate (confounding)	Intervention: Development of quality indicators (structure, process, outcome), auditing, training, introduction of new asthma encounter form. Personalized feedback and performance reports. Control: No intervention/ Before	- Decreased frequency of asthma relapse to 7.83% from 12.18% ($p<0.001$) and compared to the frequency of asthma relapse across the New York City Health Hospitals (12.79%). - Decreased asthma admission rate (3.90 from 4.85 per 100 ED visits, $p<0.02$).	
Chouaid 2004 France, 2.5 years intervention.	Before-after study. ED in a tertiary teaching hospital, 263 asthma patients RoB: Serious (outcomes' selection and confounding).	Intervention: Quality improvement program including auditing, local guidelines development, validation and distribution, staff training and feedback. Control: Before		- Significant improvement in the recording of recent medical history (100% from 68.7%), risk factors (100% from 63.5%), completion of the care pathway (94.5% from 27.8%). - Significantly improved documentation of the respiratory rate (81.8% from 36.5%), oxygen saturation (98.1% from 84.3%), and initial PEFR (98.1% from 19.1%). - Significantly improved prescription practices. - Follow-up was booked for a higher proportion of discharged patients (74.4% from 41.3%). - Significant increase in the documentation of drug prescriptions in the short term (85.1% from 67.3%), which however was not maintained 2 years later (41.9%).

Dalcin 2007 Brazil, 5 years (1 year baseline, 3 intervention, 1 post-intervention)	Before-after study. Adult ED, 500 asthma patients. RoB: Moderate (confounding).	Intervention: Development, validation, implementation and revision of a clinical pathway, annual audit, educational activities, and day to day progress monitoring. Control: Before.	- No effect on admission rate, ED discharge rate or death rate.	- Significant increase in pulse oximetry use (97% from 8.3%) and PEFR use (48% from 4.6%). However, the later decreased significantly during the last year, after discontinuation of the training process (29.7%). - Significant increase in the proportion of patients receiving three inhalations of treatment within the first hour (35.6% from 22.2%). - Significant increase in the use of oral versus IV corticosteroids (42.6% from 8.3%). - Reduction in the length of stay in the ED (8.4±10.1 hours from 12.4±17.0 hours, p= 0.04).
Doherty 2006 Australia, 14 months (7 baseline, 7 post-intervention)	Cluster RCT. 8 small rural hospitals, 187 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Quality improvement process based on the identification of evidence-practice gaps and barriers, guidelines development, reminders, education, audit and feedback. Control: No intervention.		- Significant increase in the proportion of patients whose asthma severity was assessed (62% from 8%), who had spirometry (62% from 12%), and those who received an asthma action plan (26% from 9%) and a trend over increased systemic steroid prescription (72% from 61%) in the intervention but not the control group. - Trend over decrease in the administration of ipratropium for mild asthma attacks (30% from 44%), in the intervention but not the control group. - Interestingly, a non-significant decrease in antibiotics prescription was observed in the control group (13% from 27%), with no change in the intervention group
Doherty 2007 Australia, 16 months (4 baseline, 12 post-intervention)	Comparative cohort with concurrent and historical control. 2 EDs in small rural hospitals, 215 asthma patients. RoB: Serious (outcomes' selection and confounding)	Intervention: Quality improvement process based on the identification of evidence-practice gaps and barriers, guidelines development, reminders, education, audit and feedback. Control: No intervention/ before.		- Significant increase in the proportion of patients whose asthma severity was assessed (99% from 27%), who had a spirometry or PEFR assessment (85% from 38%), who were offered an MDI with spacer (57% from 16%), those who received systemic corticosteroids (84% from 65%) and an asthma action plan (82% from 14%), in the intervention but not in the control hospital. - Significant decrease in the proportion of patients receiving SAMA for a mild exacerbation (16% from 43%) and in the proportion of patients receiving antibiotics (6% from 37%), in the intervention but not the control group.

				- Use of spirometry was increased both in the intervention (84% from 38%) and control hospital (40% from 2%).
Edmond 1998 USA, 1.5 year (6 months before, 12 during the intervention)	Before-after study. Urban teaching hospital, 196 asthma patients. RoB: Serious (confounding)	Intervention: Quality improvement process based on the identification of evidence-practice gaps and barriers, goal setting, guideline development and validation, education, reminders. Control: Before	- Progressively decreased hospital admission rate (19% from 35%, p<0.05). - No significant difference in the proportion of patients relapsing within 30 days from the ED visit (p=0.35)	- Median length of stay in the ED decreased by 58 minutes (p=0.01) and the proportion with a stay of less 4 hours increased consistently after the intervention (79% from 59%). - Significantly more patients had a baseline (83% from 20%) and follow-up (62% from 22%) PEFR measurement, while the median time until the first SABA was decreased from 22 to 6 minutes (p<0.001) - Median time until systemic corticosteroid administration did not change significantly.
Foster 2007 UK, 1 year.	Cluster RCT. 23 general practices, 545 asthma patients. RoB: High (selection, performance, detection, reporting bias)	Intervention: Quality improvement process including audits, practice development plans, multi-disciplinary training workshops and feedback of audit data. Control: Delayed implementation of the intervention (by 6 months).		- No difference in PEFR documentation at 6 months, but early intervention resulted in higher PEFR evaluation at 12 months (66% versus 36%, p<0.001). Gradual increase PEFR use over time in the intervention group (baseline: 15%, 6-months: 33%, 12-months 66%). The delayed group had a better baseline (44%) which did not improve over time. - Significant improvement of the adjusted, combined assessment scores at 12 months (p=0.02). - No significant differences in the combined management and follow-up scores.
Pinnock 2003 UK, 9 months (3 months baseline, 3 months post-intervention)	Before-after study. 4 primary care health centres, 258 asthma patients RoB: Serious (outcomes' selection and confounding)	Intervention: A quality improvement project including auditing and feedback, as well as an educational symposium and a workshop to facilitate multidisciplinary discussion. Control: Before		- General practices: Increase in the proportion of patients invited for follow-up (73% from 59%) and increased oxygen use (20% from 0%). - Out-of-hours services: Improved assessment of asthma attack severity (41% from 5%). - Nurse led walk-in clinic: PEFR more often compared with predicted value.
Stell 1996 UK, 14 months (2 months during the intervention, 1 10 months	Before-after study. 1 ED, 172 asthma patients. RoB: Serious (outcomes' selection, attrition and confounding)	Intervention: Continuous cycles of clinical audit. Results presented to staff, weaknesses discussed and methods for improvement were considered.		- Significant decrease in the use of nebulisers (88% from 97%), but consistent use of oral steroids. - Less patients had chest X-rays (43% from 73%), ABGs (33% from 73%) [these were recommended]. - Less patients had their inhaler technique checked (7% from 13%), were given PEFR meter (5% from 8%), were

interval, 2 months post-intervention)		Control: One year later, after the audit programme had ended and most medical staff had changed.		discharged on systemic steroids (when recommended, 53% from 63%), received follow-up plans (28% from 35%). - However, there was an increase in the regular treatment step-up, when required (34% from 20%).

* ABG: Arterial blood gases; ED: Emergency Department; PEFR: Peak expiratory flow rate

Table e76 Differences in the adherence to asthma guidelines by Specialists or Generalists.

Study	Design, Size, Quality	Clinical outcomes	Adherence outcomes
Diagnosis, assessment and maintenance treatment			
Abdulwadud 1999 Australia, 6 months. Specialists at the hospital vs GPs.	Single centre observational study. 1 tertiary hospital asthma clinic and nearby general practices, 105 asthma patients. RoB: Serious (outcomes' selection and confounding)		- Asthma knowledge was significantly higher among patients reviewed by GPs (p=0.002). - Patients reviewed by specialists had worse baseline quality of life, which however improved significantly during follow-up. Quality of life did not significantly improve among patients reviewed by GPs. However, there was no significant between group difference in quality of life change from baseline. - Patients seen by specialists significantly improved their self-management skills, in contrast to the control group. However, there was no significant between group difference.
Chou 2015 Taiwan, 10 years. Pulmonologists and allergists vs internists and GPs.	Longitudinal prescription trends and guidelines adherence analysis from a health insurance database. 4,495 asthma patients. RoB: Serious (outcomes' selection and confounding)		During the observation period, a steep increase was observed in the prescription of fixed dose combinations by asthma specialists (58.3% from 13.2%), which was significantly less pronounced among non-specialists. Moreover, specialists increasingly favoured inhaled over oral corticosteroids (70% from 50% of all patients received ICS and 20% from 30% were still receiving oral steroids). On the other hand, generalists prescribed ICS in only around 20% of their patients.
Erickson 2005 USA, ~2.5 years. Pulmonologists and allergists vs GPs.	Prospective observational cohort. One care organization, 4,742 asthma patients. RoB: Serious (confounding)	- Evaluation by a specialist after an acute asthma attack did not decreased future risk of asthma attacks. However, assessment by both an allergist and a pulmonologist was associated with reduced risk of subsequent ED visits for asthma (HR 0.37 [0.19-0.69]). - Evaluation by an allergist did not affect future hospitalization rate. However, review by a pulmonologist (HR: 0.74 [0.55-0.99]) or by both specialties (HR: 0.52 [0.29-0.93]) decreased future hospitalization rate.	

Frieri 2002 USA, 1 year. Allergists & immunologists vs primary care physicians,	Single centre audit. 1 University Hospital, 30 asthma patients. RoB: Serious (outcomes' selection and confounding)		- Allergists & immunologists prescribed more ICS (100% vs 80%) and had a lower LABA to ICS use ratio (0.83 vs 1.60, indicative of higher guideline adherence). - Allergists & immunologists diagnosed allergic rhinitis more frequently (80% vs 13%) and performed skin testing to identify allergy triggers in all patients (100% vs 0%). - Allergists & immunologists obtained PEFR values for all their patients (100% vs 0%). They performed spirometry for more patients (14/15 vs 9/15).
Harmsen 2010 Denmark, 3 years. Pulmonologists vs GPs	RCT. 308 asthma patients, 1 General Hospital. RoB: High (randomization [unclear], concealment, blinding, attrition bias)	- Asthma severity scores were more frequently unchanged or worse in GP vs pulmonologists groups (67% vs 45%, p<0.01). Rhinitis symptoms were similar between groups. - AQLQ and RQLQ scores were significantly improved in the pulmonologists group compared to baseline and compared to GPs, but the change did not exceed MCID. - Unchanged lung function measurements at 3-year follow-up visit in both groups.	
Kanter 2002 USA, 1 year Allergists vs GPs	Observational study. 2 allergy and 2 general practices, 119 asthma patients. RoB: Serious (confounding)	- Patients reviewed by allergists reported improved health related quality of life in all SF-36 domains. In five SF-36 domains, the change from baseline was significant higher for patients reviewed by allergists vs GPs (role-physical, bodily pain, general health perceptions, vitality and social functioning, P<0.05). - Review by allergist was also associated with statistically significantly higher mean improvement from baseline in the symptom-free index, functioning with asthma, asthma energy scales and total score of the ITG asthma short form. - No between group differences in the number of physician visits or hospitalizations.	- Patients treated by allergists were receiving more often oral or nasal/ inhaled corticosteroids/ anti-inflammatories.

Meng 1999 USA. Asthma Specialists vs generalists.	Cross-sectional study. 8 health regions in 7 states, 6703 asthma patients RoB: Serious (participants' selection, confounding)	- Under specialists care, more patients receive <8puffs of inhaler per day (1.25, p<0.05).	- Regular use of inhaled steroids is prescribed more frequently by specialists (OR: 2.57, p<0.01). - Under specialists' care, more patients measure their peak flow regularly (OR 4.83, p<0.01) and had an allergy evaluation (OR: 3.16, p <0.01)
Morishima 2011, Japan. Pullmonologists or allergists vs non-specialists	Cross-sectional study. Insurance claims database in Kyoto, 13,428 asthmatics. RoB: Low		- Specialists were more likely to prescribe ICS (aOR: 2.70, [2.46-2.97].
Schayck 1989 Netherlands. Pulmonologists vs GPs	Cross-sectional study. 29 general practices, 233 asthma patients. RoB: Serious (outcomes' selection and confounding)		- Pulmonologists prescribed six time more ICS than GPs. In general, they prescribed more medications that GPs. - Pulmonologists prescribed higher doses of ICS for more severe asthma, while GPs prescribed more bronchodilators. - 20% and 16% of those treated by pulmonologists or GPs, received treatments for which they did not respond, at least at the time of testing.
Tada 2015 Japan. Pulmonologists vs GPs	Cross-sectional study. 39 private clinics and 9 general hospitals. 860 asthma patients. RoB: Serious (confounding)	- Older patients with more severe asthma (GINA 3-5) and younger patients under the care of pulmonologists achieved better disease control (ACT, p=0.048), compared to those treated by GPs. - Older patients with milder asthma (GINA 1-2) under the care of GPs achieved better control. - Elderly asthmatics under the care of GPs used fewer rescue inhalers compared to those treated by pulmonologists. However, those treated by GPs had in general less severe disease and the study results were not adjusted.	
Vollmer 1997 USA.	Cross-sectional study.	- Allergists' patients had improve quality of life as measured by several dimensions of the SF-36 scale (p <0.05).	- Patients receiving primary asthma care by allergists were more often using inhaled anti-inflammatory agents, oral

Allergists vs GPs.	1 Health maintenance organization (Kaiser Permanente, Portland). 914 asthma patients RoB: Serious (confounding, attrition bias).		steroids and regular inhaled medications to control their asthma (p<0.01). - Allergists' patients were more likely to have asthma exacerbations treated in a clinic setting rather than the emergency department (p<0.01).
Wu 2001 USA, 2 years. Pulmonologists, Allergists or experienced generalists vs generalists	Cohort study 12 managed care organizations, 1,078 physicians, 1,954 asthma patients. RoB: Serious (confounding)	- Overall, specialists or experienced generalists care was associated with less ED visits, hospitalisations and missed days of work. - Patients under the care of pulmonologists specifically, had more hospitalizations, but reported better quality of asthma care, suggesting the increased hospitalization may result from a more severe asthma.	- Specialists and experienced generalists more often offered allergy evaluation, peak flow meter at home, prescribed ICS and oral corticosteroids, discussed asthma triggers and offered asthma education. - On the other hand, these patients were more often overusing SABAs.
Zeiger 1991 USA. 6 months follow-up. Asthma specialists vs general physicians.	RCT. 1 Health maintenance organization (Kaiser Permanente, San Diego). 309 asthma patients. RoB: High (selection, performance, detection bias).	Management by asthma specialist was associated with: - 75% reduction in night awakenings (p<0.001). - Almost 50% reduction in asthma attacks leading to an emergency presentation (p=0.017). - Reduction in the frequency of asthma attacks (p = 0.005)	- Inhaled corticosteroids (p<0.001) and cromolyn (p=0.002) were prescribed more often by asthma specialists compared to control.
Diagnosis, assessment and management of acute attacks			
Bell 1991 UK, 2 years. Pulmonologists vs internists.	Single centre audit. 76 asthma patients, 1 district general hospital. RoB: Serious (outcomes' selection and confounding)		- Prescription patterns: Chest physicians administered emergency treatments (SABA & systemic steroids) more often within the target timeframe, and tailored treatment to response more effectively. There were no between-group differences in antibiotic prescription practices. - Specialists organized OPD follow-up more frequently. Specialists recorded severity measures more accurately.
Pearson 1996 UK, 2 years.	Audit. 36 teaching and district hospitals, 1,666 asthma patients.		- Pulmonologists were more likely to assess pCO2 on arrival, to prescribe systemic steroids within 24 hours from presentation, to assess PEFR variability, to prescribe oral steroids on discharge, to organize an outpatient

Pulmonologists vs general physicians.	RoB: Serious (outcomes' selection and confounding)		appointments, and to provide a self-management plan (p<0.05).
Pellicer 2001 Spain. Pulmonologists vs GPs	Cross-sectional study. 96 outpatients that have been assigned an asthma diagnosis by a pulmonologist or GP. RoB: Low	- Diagnosis by a pulmonologist did not significantly differ from the final diagnosis based on rigorous evaluation of clinical characteristics and relevant laboratory tests / biomarkers. However, GP diagnosis differed significantly from the final diagnosis.	

* GPs: General practitioners, OPD: Outpatient department, PEFR: Peak Expiratory Flow Rate.