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PRESENCE OF MODIFIABLE FACTORS RESTRICTING THE EFFECTIVENESS OF TREATMENT IN POORLY CONTROLLED PATIENTS WITH ASTHMA

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Abstract

Several modifiable variables that lead to poor control of asthma have been identified. The goal was to assess the percentage of patients with insufficient care, adherence to it or critical inhaler technique errors, and their effect on the control of asthma. For the first time, we carried out a cross-sectional multicenter retrospective analysis including asthma patients who were referred from primary to specialist care. According to recommendations, medication adherence, and disease prevention, the data collected was properly prescribed. of the 1682 patients (age 45 ± 17 years, 64.6 percent males), 35.9 percent had insufficient prescription, 76.8 percent had poor adherence, and 17 percent had critical inhaler errors, with slightly less critical errors among users of Easy haler than other users of dry powder inhalers (10.3% versus 18.4%; $p < 0.05$). Inadequate dosage (OR: 3.65), non-adherence to medication (OR: 1.8), and inhaler misuse were factors linked to poor asthma control (OR: 3.03). A larger number of risk factors have been associated with a higher likelihood of poorly managed asthma.

Keywords: Modifiable factors, Asthma, Inhaler technique.

Introduction

Asthma is a common disorder which accounts for substantial healthcare costs and a loss of productivity at work. According to a report published in 2015, its prevalence is rising worldwide: almost 1000 people die from asthma every day. Latest statistics on global asthma prevalence suggest that it affects 334 million individuals worldwide. Its prevalence, however, varies significantly between countries with the highest prevalence seen in advanced ones. Exacerbations are particularly correlated with high direct (medications, hospitalization, emergency room treatment, and indirect (school absenteeism, loss of work efficiency, etc.) costs. Asthma exacerbations are actually one of the most common triggers of visits to the Emergency Department to emphasize inadequate asthma control in affected patients. Many factors can induce an exacerbation: in the case of uncontrollable asthma, exposure to environmental factors, inadequate adherence to medication, insufficient therapy, and poor inhaler technique are among the most important modifiable causes (1). In asthmatic patients, several studies have shown poor treatment adherence: <50 percent in children and 30-70 percent in adults, depending on region, age, sex, and ethnicity. Restricted understanding or recognition (among patients and/or physicians), attitudes or side effect issues, inhaler properties, and guidelines for their use were the reasons for this variation. The main aspect of poor asthma control is often that many patients are undertreated, particularly with mild to moderate asthma (2). Thus, as a clinical target, asthma management is far from being accomplished. Better management will not only boost cost efficiency, but also quality of life, decrease school absenteeism, and also increase job productivity. In primary care treatment of asthma, the same situation is mirrored. Several research on asthma in primary care seem to indicate that, despite available treatments, asthma management in clinical practice is suboptimal. Over the past few years, European publications have reported no obvious change in symptom management. The primary goals of this research are to assess the adequacy of the recommended medication as well as the presence of inadequate adherence and essential inhalation technique errors in patients first referred to a specialist from primary care; and to study the relationship between these factors and poor control of asthma (3).

Material and Methods

Study design and participants

A cross-sectional multicentre retrospective study was performed in patients aged 18 years or older who used some form of inhaler device and were first referred for some kind of purpose from primary care to a pneumologist or allergologist. The data was gathered between September and December 2016. The exclusion criteria were the absence of signed informed consent and incapacitating disease or mental illness, which made it impossible to participate in the study according to the research criteria. In order to confirm/exclude the diagnosis of asthma, both patients underwent spirometry and a bronchodilator examination.

Study measurements

The following key variables were evaluated: effective management of asthma according to GINA recommendations (GINA treatment measures 1-5 were used to determine the adequacy of current patient treatment based on asthma control at the time of the visit (4). GINA standards for asthma management were used for this evaluation, as explained below), medication adherence according to the MG questionnaire (patients were graded as reliable or unreliable according to the 0 to 4 punctuation, where 0 = reliable and < 1 = unreliable), inhaler adherence (TAI < 50 reliable; <50 unreliable) and critical errors with patient inhaler technique. In addition to finding vital errors by the practitioner, this item consists of a practical demonstration of patient inhaler technique. This item shows 2 patient categories: with < 1 or without crucial errors. A questionnaire from the GEMA instructional material 477 assessed additional patient information about asthma (Supplementary Table 3). In addition to finding vital errors by the practitioner, this item consists of a practical demonstration of patient inhaler technique. This item shows 2 patient categories: with ≥ 1 or without crucial errors. A questionnaire from the GEMA instructional material 477 assessed additional patient information about asthma (Supplementary Table 3) (5). Asthma incidence according to the 2015 GINA criteria44, comorbidities (allergy, occupational exposure to allergens or irritants, smoking, etc and asthma management according to both GINA and ACT criteria were the following clinical data collected. According to GINA, the following things were taken into account: day/night symptoms in patients (<2 times/week daytime symptoms and no night time symptoms), symptom relief therapy (<2 times/week) and no movement limits in the past 4 weeks. Patients were then divided into 2 categories: well-controlled with all previous items), partially/not controlled (with 1-4 previous items). Patients were grouped into the same 2 groups according to the ACT, but in this case they were defined by 5 items of the ACT validated Spanish version (almost 21: well managed, <21: partly/not controlled). Patients with a body mass index >30 have been diagnosed as being obese.

In a single visit, all data was obtained through an online patient diary, proportionate to the needs of the research. The approval of the Ethics Committee (Hospital Clinic de Barcelona, Registration number HCB/2016/0647) was obtained and the research was carried out in compliance with the Declaration of Helsinki (1964). Informed consent from all participants was obtained (6).

Statistical analysis

Statistical inference was analyzed for categorical data using the Pearson chi-squared test ($\chi 2$) and for continuous data using variance test analysis. In order to determine the independence of detected variables, a binary logistic regression was used (OR). Cohen's k coefficient, Spearman's correlation coefficient, and R square were expressed through the relationship and agreement between ACT/GINA on asthma regulation (R2). All data was analysed using version 20.0 of SPSS.

Results

The number of patients involved in the study was 1682, 64.6 percent of whom were males. There was a mean age of 45 ± 17 years. Table 1 displays the features of the cohort.

Table 1 Baseline demographic and clinical characteristics.

From: Prevalence of modifiable factors limiting treatment efficacy of poorly controlled asthma patients: EFIMERA observational study

Variable	Results	Number of patients evaluated
Age (years), mean ± SD (range)	45.2 ± 17.9 (18–90)	1681
Females, *n* (%)	592 (35.4)	1670
Males, *n* (%)	1078 (64.6)	1670
Age at diagnosis (years), mean ± SD	33.8 ± 15.7	1682
Disease duration (years), mean ± SD	14.9 ± 14.1	1682
Time between treatment initiation and diagnosis (years), mean ± SD	1.1 ± 6.6	1677
Current smokers, *n* (%)	263 (15.7)	1678
Ex-smoker, *n* (%)	294 (20.8)	1414
Any allergy, *n* (%)	665 (39.8)	1671
Any comorbidity, *n* (%)	841 (50.4)	1668
Obesity, *n* (%)	242 (14.5%)	1668
Rhinosinusitis, *n* (%)	190 (11.4%)	1668
Rhinitis/conjunctivitis, *n* (%)	313 (18.8%)	1668
Gastroesophageal reflux disease, *n* (%)	149 (8.9%)	1668
Other comorbidities, *n* (%)	268 (16.1)	1668
Predicted FEV_1 (or personal best PEF value), *n* (%)		
≥80%	1042 (62.3)	1673
<80%	507 (30.3)	1673
<60%	124 (7.4)	1673
Categories of asthma severity (2015 GINA), *n* (%)		
Mild	719 (42.9)	1674
Moderate	780 (46.6)	1674
Severe	175 (10.5)	1674
Level of asthma symptom control (2015 GINA)		
Well controlled	474 (28.2)	1679
[a]Partly controlled	635 (37.8)	1679
[a]Uncontrolled	570 (33.9)	1679
Current treatments, *n* (%)		
Only maintenance inhaler	492 (29.6)	1662
Only rescue inhaler	357 (21.5)	1662
Maintenance inhaler + rescue inhaler	468 (28.2)	1662
Maintenance inhaler + oral treatment	78 (4.7)	1662
Rescue inhaler + oral treatment	40 (2.4)	1662
Maintenance inhaler + rescue inhaler + oral treatment	206 (12.4)	1662
Monoclonal antibodies	23 (1.4)	1662
Type of maintenance inhaler device, *n* (%)		
Multiple-dose DPI	935 (75.2)	1244
pMDI	240 (19.3)	1244
Single-dose DPI	26 (2.1)	1244
pMDI + multiple-dose DPI	39 (3.1)	
pMDI + multiple-dose DPI	39 (3.1)	
pMDI + single-dose DPI	4 (0.3)	1244

Modifiable factors associated with asthma control

35.9 percent of patients have an insufficient or inadequate medication, according to the Global Initiative for Asthma (GINA) guidelines (Table 2). GINA 1-5 steps were taken into consideration in order to determine whether the drug was adequate or not. In order to determine whether the care was satisfactory or not the maintenance treatment of patients was correlated with their exacerbations in the past and their current symptoms according to these 5 GINA steps. Of these patients with insufficient medication, 82.5% had poorly regulated (partly/uncontrolled) asthma (according to the Asthma Control Test (ACT), while 56.3% had poorly controlled asthma in patients with adequate care (odds ratio (OR) 3.65, 95% confidence interval (CI): 2.87-4.65, p < 0.0001; Table 3) (7-10).

Table 2: Prevalence of modifiable factors associated with asthma control

Factor	*n* (%)	Number of patients evaluated
Inadequate prescription (GINA)		
Yes	604 (35.9)	1681
No	1077 (64.1)	1681
Adherence according to Morisky–Green questionnaire		
Adherent	522 (31.5)	1658
Non-adherent	1136 (68.5)	1658
Adherence according to TAI		
Adherent	381 (23.2)	1639
Non-adherent	1258 (76.8)	1639
Critical inhaler mistakes		
No errors	1394 (83.0)	1680
≥1 error	286 (17.0)	1680

GINA Global Initiative for Asthma, *TAI* Test of Adherence to Inhalers.

Table 3: Relation between asthma control by ACT criteria and modifiable factors associated with poor control.

From: Prevalence of modifiable factors limiting treatment efficacy of poorly controlled asthma patients: EFIMERA observational study

Modified factor	Control (ACT criteria)		OR (95% CI)	*n* (%)	*p*
	Poor	Good			
Prescription					
Inadequate (A)	498 (82.5%)	106 (17.5%)	3.65 (2.87–4.65)	604 (36)	<0.0001
Adequate	606 (56.3%)	471 (43.7%)		1077 (64)	
Adherence (TAI)					
Poor (B)	866 (68.8%)	392 (31.2%)	1.80 (1.42–2.27)	1258 (74.7)	<0.0001
Good	210 (55.1%)	171 (44.9%)		381 (22.7)	
Critical mistakes					
One or more (C)	238 (83.2%)	48 (16.8%)	3.03 (2.18–4.21)	286 (17.0)	<0.0001
None	865 (62.1%)	529 (37.9%)		1394 (83.0)	
A + B	399 (85.2%)	69 (14.8%)	4.16 (3.14–5.50)	468 (27.8)	<0.0001
A + C	119 (90.1%)	13 (9.9%)	5.23 (2.92–9.36)	132 (7.8)	<0.0001
B + C	202 (84.9%)	36 (15.1%)	3.36 (2.32–4.86)	238 (14.1)	<0.0001
A + B + C	101 (93.5%)	7 (6.5%)	8.23 (3.80–17.83)	108 (6.4)	<0.0001

76.8 percent of patients had a poor adherence measured by the Test of Adherence to Inhalers (TAI) questionnaire and 68.5 percent by the Morisky-Green (MG) questionnaire with respect to medication adherence (Table 2). In addition, 68.8% of poorly adherent patients had poorly controlled asthma (according to the ACT), while 55.1% had poorly controlled asthma despite strong adherence (OR 1.8, 95% CI: 1.42–2.27, p < 0.0001; Table 3) (11).

Nearly 17% of patients had at least one of the critical errors (errors in the usage of the system that impair the efficacy of inhaled therapy) in the inhaler technique, as assessed by the extended TAI test (Table 2); among patients with critical errors, 83.2% had poorly controlled asthma (according to the ACT), compared with 62.1% with poorly controlled asthma and no critical errors. A pressurized metered dose inhaler (pMDI) or dry powder inhaler (DPI) was observed, with a different percentage of misuse depending on the unit. In Easyhaler (EH) users, substantially less critical errors were observed

compared to other DPI users (Table 4), (EH: 10.3 percent; other DPI: 18.4 percent; p < 0.05): 10.3 percent of patients had critical EH errors, 19.5 percent with Accuhaler, 16.0 percent with Nexthaler, and 17.5 percent with Turbuhaler (p < 0.01). As a result (Table 4), the need for technique change was substantially lower (Table 4). Compared to other DPIs, a substantially lower need for technique adjustment was observed for EH users (p<0.0001; Table 4).

Table 4: Number of critical mistakes and need of technique adjustment according to DPI device

From: Prevalence of modifiable factors limiting treatment efficacy of poorly controlled asthma patients: EFIMERA observational study

DPI device	Critical technique mistakes, *n* (%)	Need of technique adjustment, *n* (%)	Number of patients evaluated
Accuhaler	30 (19.5)	106 (68.8)	154
Easyhaler	13 (10.3)	43 (34.4)	126
Nexthaler	17 (16.0)	52 (51.5%)	106
Turbuhaler	36 (17.5)	120 (58.3%)	206

DPI dry powder inhaler.

Asthma control

71.7 percent of patients had poorly controlled asthma according to the GINA criterion and 65.7 percent according to the ACT test with respect to asthma control. According to the GINA criteria and the ACT evaluation, many factors have been shown to be linked to poor asthma control (Table 3): insufficient prescription: (GINA: OR 1.58, 95% CI: 1.23–2.03; ACT: OR 1.8, 95% CI: 1.42–2.27), and inhaler misuse (GINA: OR 4.76, 95% CI: 3.08–7.34; ACT: OR 3.03, 95% CI: 2.18–4.21).

Each of these risk factors (insufficient prescription, inadequate enforcement and abuse of the inhaler) has a statistically important effect on poor control of asthma ($p < 0.0001$; Table 3).

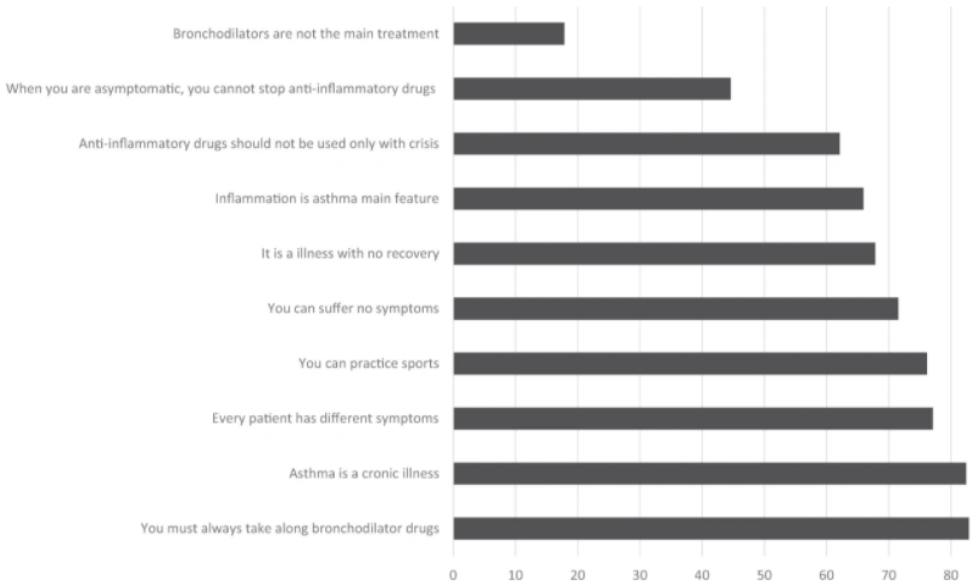
Asthma regulation according to the GINA score showed a mild concordance (Kappa = 0.458; Rho = 0.709; r2 = 0.503) compared with the ACT questionnaire score. Supplementary Tables 1 and 2 and Supplementary Figures 1 and 2 display the related tables for GINA asthma control, which are very similar to ACT control (12).

Asthma knowledge questionnaire

As to the the asthma awareness questionnaire, during both exacerbation and recovery periods, the troublesome questions appeared to be linked to asthma care (Fig. 1): only 17.8 percent of patients understood that bronchodilators were not the primary treatment for asthma, and less than half of patients knew that maintenance treatment had to be continued during remission periods. While less than half of the patients were aware of the proper use of anti-inflammatory medications, >60% they understood that it could not only be used in crisis cases, and they knew that asthma was an inflammatory condition (13). About 80 percent of patients knew that asthma was a chronic condition, and 70 percent knew they could play sports and have no symptoms at all. But most of them struggle with poorly controlled (and therefore symptomatic) asthma (as discussed above). When the influence of asthma awareness on asthma management was measured, despite the undoubted effect of these myths on adherence to care, depending on the ACT parameters, it was found to be an independent indicator of impaired regulation of asthma (Fig. 2) (14).

Fig. 1: Asthma knowledge questionnaire.

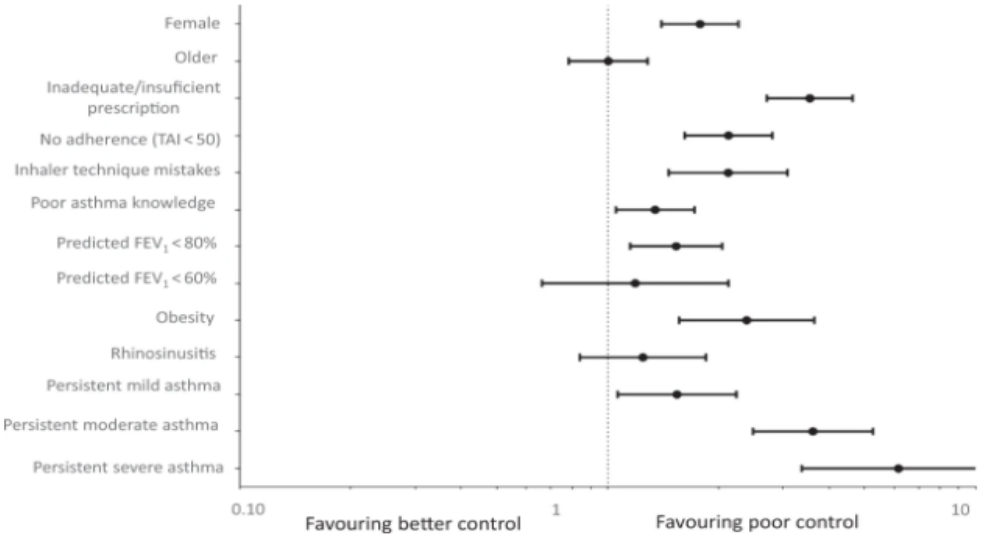
From: Prevalence of modifiable factors limiting treatment efficacy of poorly controlled asthma patients: EFIMERA observational study



Percentage of correct responses to asthma knowledge questionnaire (self-administered).

Fig. 2: Binary logistic regression model with poor asthma control (ACT < 21) as dependent variable.

From: Prevalence of modifiable factors limiting treatment efficacy of poorly controlled asthma patients: EFIMERA observational study



This figure represents factors associated with poor asthma control.

Discussion

Despite years of adoption of asthma guidelines, inadequate asthma regulation remained strongly correlated with modifiable features linked to therapy failure in this study. According to previous publications, while several factors may be involved in poor asthma control, three factors tend to be the key causes of poor primary care asthma control: insufficient prescription, poor adherence to medication, and poor inhaler technique. Obesity has a detrimental effect on asthma, and preliminary results suggest the impact of reducing weight on the control and quality of life of asthma (15). The recommendation for diet-induced weight loss in patients with asthma, however is connected to a multitude of general health benefits, but there is still inadequate evidence for asthma control,18 for which the authors did not include this factor in the modifiable ones.

71.7 and 65.7% of patients (according to GINA and ACT, respectively) showed impaired symptom management in our study. During the past years, numerous studies have been performed in primary care with various observable variables and design16. Both displayed the same propensity towards weak asthma regulation, despite their heterogeneity (16). Calvo et al. 1919 In a recent Spanish publication, In 638 asthmatic patients, inadequate asthma control (ACT ?? 20) was found to range from 23.4 to 75.6 percent depending on the medical consultation of the patients. Almost half of the patients, on average, displayed poor control. The authors of another study20 reported that no controlled asthma was present in 45% of asthmatic patients who received some form of treatment in Spain (ACT < 19). Asthma control was measured according to the Asthma Control Questionnaire in the European LIAISON Study: the percentage of patients with partial or non-controlled asthma was 56.5 in 12 participating countries. The situation is similar in the United States: 50 percent of patients who attended primary care for non-respiratory consultation had asthma that was not regulated (ACT < 19). Compared with our research, most reports indicate a significantly lower percentage of poorly managed patients. As patients referred to specialist treatment are not expected to be asymptomatic, this may possibly be attributed to preference bias (17).

More than one third of our patients had insufficient medication at the time of referral to primary care, which was associated with less adequate control of asthma. Asthma severity is likely to be underestimated by both clinicians and patients, which may be the reason that many patients may be undertreated.

Lack of time and economic resources are some of the reasons why asthma management in the primary care setting is not completely satisfactory, although it is well known that inadequate diagnosis and treatment is harmful to the health of patients, which in turn raises the demand for care and the cost of health. In this context, ACT was developed as a method for detecting poorly regulated asthma and as a result, recognizing those patients that need the most suitable care. It has been shown that when the doctor regularly uses it, it makes a smoother care change.

Electronic devices, which may be the gold standard8, (they are an objective tool for assessing the adherence of patients), are the best technique for evaluating adherence, but for many patients they are costly and difficult to use. The most cost-effective measure to test it seems to be self-reports, although patients are reluctant to disclose weak adherence on certain occasions. Two compliance

questionnaires were used in this analysis, and the TAI questionnaire appears to be more sensitive than the MG one (76 and 68.5 percent , respectively, have a poor adherence). It is also seen that the TAI has a stronger relationship with actual patient adherence. Moreover a statistically significant association with weak adherence (ACT OR 1.8; GINA OR 1.58) is observed when asthma regulation is compared according to the ACT punctuation and the GINA criteria. Similarly, almost 50 percent of patients in the Identify Asthma and LInk to Symptoms and Experience (REALISE) study11 reported weak adherence to medication and a higher rate of low adherence (according to MG) was found in the LIAISON study in patients with poorly regulated asthma relative to those with controlled asthma. It should be noted that its absence is correlated with a higher risk of asthma exacerbations, increased use of oral corticosteroids, need for emergency department attendance and/or hospitalization, degradation of forced expiratory volume in 1 s values, and consequently higher costs and poor quality of life7, to emphasize the significance of good adherence. Strategies for improving adherence have been discussed, such as regularly updating the technique of inhaler use and patient adherence during each visit. Electronic reminders can also be used, as 29,30,32,33 can be very effective. In primary care, it was developed that in terms of improving adherence, monitoring, and reducing costs, an educational program could be successful (18).

With regard to the third significant factor responsible for poorly controlled asthma, insufficient inhaler technique, this study found that 17% of primary care patients make critical errors and are directly linked to impaired asthma control (GINA OR 4.76; ACT OR 3.03). Serious errors in the technique of the inhaler can be identified as errors that potentially restrict drug uptake and its distribution to the lungs12. The percentage of critical errors in some studies is higher than that in our study (ranging from 50 to 90 percent); however this step remains unquestionably crucial in order to achieve asthma control. A poor inhaler technique has been shown to be associated with more symptoms, greater need for hospitalization12, and definitely less effective control of asthma.

Asthma awareness and comprehension findings are not promising and are noteworthy causes of inadequate control of asthma: most patients conclude that bronchodilators are the primary therapy for asthma management and that during recovery times, anti-inflammatory treatment should be avoided. It tends to be an independent indicator of asthma control when asthma comprehension is evaluated as a predictive factor of asthma poor control via a binary logistic regression. These issues probably affect the adherence of patients: half of the patients did not take their maintenance medications correctly in the REALISE study11, and 50 percent did not take maintenance medications as prescribed among patients with poor control because they felt it was not necessary. Nearly 50 percent of patients in another study10 believed their asthma was well managed, even though they had extreme and persistent symptoms (19).

Conclusion

Bad asthma management, medication adherence, inhaler procedure, and poor awareness of asthma are important factors that result in decreased asthma control at the level of primary care. Many patients do not receive appropriate care, even when referred to a doctor, adherence to therapy is low. Furthermore, it is a common finding that patients show crucial errors in the inhaler technique.

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