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Cost analysis of GER-induced asthma: A controlled study vs. atopic asthma of comparable severity

Roberto Walter Dal Negro[a,b,*], Paola Turco[a], Claudio Micheletto[a], Silvia Tognella[a], Luca Bonadiman[a], Massimo Guerriero[c], Marco Sandri[d]

[a]*Lung Department, Orlandi General Hospital, Via Ospedale, 2-37012 Bussolengo—Verona, Italy*
[b]*CESFAR—Centro Studi Nazionale Farmacoeconomia e Farmacoepidemiologia Respiratoria—Via Ospedale, 2-37012 Bussolengo—Verona, Italy*
[c]*ESI Department, Statistics Section, University of Verona, L.ge Porta Vittoria 41, 37129 Verona, Italy*
[d]*Department of Economics Faculty of Economic Sciences University of Verona—L.ge Porta Vittoria 41, 37129 Verona, Italy*

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Summary
Bronchial asthma is a costly disease: while the role of pharmaceutical strategies was greatly emphasised in order to alleviate its economic burden, the aetiological approach to asthma has received much less attention from this point of view. The impact of gastro-oesophageal reflux (GER)-related asthma was assessed in comparison to atopic asthma in 262 matched patients, and the corresponding direct and indirect annual costs calculated. All subjects were screened by means of a 95-item self-questionnaire. The overall resource utilisation was calculated for the last 12 months. Drug-induced annual costs were €290.4 (interquartile range—iqr 32.8) in atopic and €438.4 (iqr 27.8) in GER-related asthma ($p<0.001$); expenditure for medical consultations and diagnostics were €166.1 (iqr 14.8) vs. €71.6 (iqr 11.0) ($p<0.001$), and €338.4 (20.0) vs. 186.9 (iqr 26.5) ($p<0.001$), respectively. Direct costs due to hospital admissions and indirect costs due to absenteeism were also higher in GER-related asthmatics: $2.201.7\pm90.0$ vs. $€567.1\pm11.0$ ($p<0.001$), and $€748.7\pm94.7$ vs. $€103.6\pm33.9$ ($p<0.001$), respectively. The total annual cost per patient was €1246.7 (iqr 1979.6) in atopic and €3967.1 (iqr 3751.5) in GER-related asthma, $p<0.001$. In conclusion, GER-induced asthma has a more relevant economic impact on healthcare resources than atopic asthma. Although further studies are needed, present data tend to demonstrate that when facing difficult asthma (GER-related asthma in this case), the aetiological assessment of the disease plays a critical role in optimising the approach to patients' needs.

*Corresponding author. Tel.: +39 045 6712193; fax: +39 045 6712544
E-mail address: rdalnegro@ulss22.ven.it (R.W. Dal Negro).

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Introduction

Bronchial asthma is a disease which places a high burden on healthcare resources. Usually, the determination of the economic impact of bronchial asthma is based on cost-of-illness analyses, which are aimed at assessing the distribution of healthcare resources used to manage the disease.[1–4]

The role of the various therapeutic strategies has been greatly emphasised in health economic evaluations, most likely because pharmaceutical intervention is generally supposed to represent a crucial opportunity of achieving a good control of asthma[5–11] and of alleviating the economic burden of the disease.

In contrast, the role of the aetiological determinants of the disease received much less attention from this point of view, although it is well known that assessment of the precise origin of asthma can become difficult in some circumstances (i.e. when the atopic cause is excluded), independently of the therapeutic approach.

Increasing attention has been paid to bronchial asthma when related to the occurrence of acid gastro-oesophageal reflux (GER), and the causative (or triggering) role of GER was emphasised in the last decade, particularly in non-atopic subjects.[12–17] GER-related asthma represents a peculiar form of bronchial asthma which falls in the domain of both gastroenterologists and pneumologists. Although it is characterised by specific digestive symptoms (such as acid regurgitation and heartburns), the diagnostic profile and the patho-physiological pattern of this kind of asthma are still difficult to depict by pneumologists.[17]

For these reasons, GER-related asthma was included in the list of "difficult asthma forms" since long ago, and it can represent a challenging model for investigating the role of a particular aetiologic feature of asthma in affecting the disease's economic impact. At present, to our knowledge, no published data are available on the economic burden of GER-related asthma.

The aim of the present study was to assess the cost of GER-related asthma and to compare its economic impact with that of atopic asthma of the same severity.

Material and methods

A cohort study of 246 adult asthmatics naïve to our Department (172 females; mean age 47.0 ± 16.6 SD; 28 smokers of <10 packs/year; 41 ex-smokers; FEV_1 increase $\geqslant 12\%$ baseline, following inhaled salbutamol 200 mcg documented during the 6 months preceding the study) was carried out for 12 months after obtaining their informed consent. The study was approved by the local Ethical Committee during the November 11, 2004 session; protocol n. 400/6).

One hundred and forty-two subjects were assessed as asthmatics of atopic origin (positive prick test to a 12-allergen panel of inhalant allergens; Lofarma; Italy, and RAST; Immulite 2000; DPC Diagnostic Products; Los Angeles, CA, USA). All these subjects did not complain of any significant digestive symptom for years.

One hundred and twenty subjects were assessed as non-atopic (negative prick test and RAST) asthmatics who also complained of significant digestive symptoms (such as daily occurrence of acid regurgitations and heartburns, or at least $\geqslant 2$ times/week). In these cases the presence of asthma-triggering pathological acid GER was confirmed by 24-h pH monitoring (Digitrapper MKIII, Synectics Medical AB, Stockholm, Sweden) after patients' informed written consent.

When recruited, all subjects performed a further spirometrical test (according to CECA guidelines, by means of SyncMaster 510s, Jaeger, Hoeckberg, Germany) to assess their current asthma severity, which was graded according to the GINA guidelines.[18]

All subjects were investigated by means of a 95-item self-questionnaire. The questionnaire was compiled to investigate all subjects in terms of their demographics, smoke habit, clinical history (such as the type, time of onset and duration of respiratory and/or digestive symptoms), diagnostic course before assessing the cause of asthma (and the overall duration of the diagnostic procedures), and also in terms of their pharmacological history (such as the drugs taken regularly and/or when needed, their doses, and treatment duration).

The protocol just consisted in collecting data concerning the diagnostic procedures, the therapeutic approach, and the trend to hospitalisation established in all patients before the recruitment in the study, without any decisional role by the authors of the present observational survey. Any possible inconsistency with current guidelines for asthma management should be regarded as uniquely mirroring the real-life management of both atopic and GER-related asthma in general practice.

The overall healthcare resource utilisation (such as number of hospitalisations, medical visits, work days off, and costs for diagnostic tests and drugs) was calculated in each subject for the last 12 months. Before the study start-up, the questionnaire was tested in a small sample of other subjects ($n = 22$) during a 2-month pilot study to assess the respondents' comprehension of the items.

Pharmacoeconomic assessment

The present study was a cohort incremental study. Costs due to drugs consumption were calculated according to the prices published by the Informatore Farmaceutico ED, OEMF, Milano, 2004.[19]

Expenditures due to visits to physicians were calculated on the basis of the fares reported in the DM 22.07.1996, Gazzetta Ufficiale n° 216, 14.09.1996.[20]

Costs due to hospitalisation were calculated on the basis of the DM 14.12.1994 and DM 30.06.1997, suppl. Gazzetta Ufficiale n° 209, 08.09.1997.[21]

Costs due to work loss were calculated for individuals currently employed, according to the indications by the Bank of Italy, 2002.[22]

Statistics

The Wilcoxon rank-sum test was used to test the hypothesis that the distribution of a quantitative variable (costs, age, etc.) is the same in the two groups of asthma subjects. The random association between a categorical variable (sex, smoke, etc.) and asthma aetiology was tested by Fisher's exact test; $p < 0.05$ was accepted as the minimum level of

statistical significance. In addition, the differences of the analytical and total (mean and median) annual costs were estimated by classical regression and quantile regression models for each type of cost: dependent variable was the logarithm of the cost and the independent variables were sex, age, basal FEV_1, respiratory signs (age of onset and duration) and the dichotomous variable atopic/GER-related asthma. By this technique we evaluated the statistical significance of the difference of the costs between the two groups (Atopic vs. GER-related asthma) taking jointly into account the effects of all the explanatory variables of the two groups.

Due to the high skewness of the distribution of costs, medians and interquartile ranges were used to describe these variables in the two subgroups of subjects. If the median value of a certain category of costs equals 0, the corresponding arithmetic mean value is reported in order to clarify the dimension of that cost.

Results

The demographic and basal lung function characteristics of the two samples of subjects are reported in Table 1.

Subjects in both subgroups were well matched in terms of asthma severity (Table 1). Atopic asthma was slightly more frequent in mild cases, while GER-related asthma was more represented in severe asthmatics.

At the recruitment stage, mean FEV_1 values were 84.9% pred. $\pm$19.3 SD in atopic and 80.8% pred. $\pm$18.4 SD in GER-related asthmatics, respectively (p = ns). Females made up 50.7% of atopic asthmatics, but were the great majority (83.3%) of GER-related asthma subjects, with the mean age of this group being significantly higher than that of atopic subjects (52.0 years $\pm$16.2 SD and 42.7 years $\pm$15.6, respectively, $p<0.001$).

In atopic asthmatics (i.e. the younger group of subjects), respiratory symptoms (i.e. coughing, wheezing, chest tightness, shortness of breath) have an earlier onset (28.2 years $\pm$17.4 SD vs. 44.5 years $\pm$17.4 SD, $p<0.001$) and a longer mean duration than in GER-related asthmatics (14.5 years $\pm$11.7 SD vs. 7.5 years $\pm$10.7 SD, respectively, $p<0.001$).

GER-related asthmatics reported a long history of digestive symptoms (i.e. frequent or daily acid regurgitation, heartburns, belching) over a long period (mean duration 15.4 years $\pm$11.0 SD), which was twice as long as that of respiratory symptoms (mean duration 7.5 years $\pm$10.7 SD) in the same subject sample ($p<0.001$). The corresponding distributions of both of these mean values are reported in Table 1.

Moreover, in GER-related asthmatics, the onset of digestive symptoms (mean value = 36.6 years $\pm$14.8 SD) systematically preceded that of respiratory symptoms (mean value = 44.5 years $\pm$17.4 SD, $p<0.05$; Table 1).

In general, the process for assessing the patients' asthma profile proved much more complicated in GER-related than in atopic asthma subjects. In particular, the number of clinical tests performed was significantly higher in GER-related asthma patients (12.0 $\pm$10.4 SD vs. 7.6 $\pm$7.0 SD, respectively; $p<0.001$). The mean number of visits to GPs made in the same period was equivalent in both groups of

Table 1 Demographic and basal lung function characteristics of subjects

	Atopic asthma	GER-related asthma	p value
Total (n)	142 (54.2%)	120 (45.8%)	
Gender: females (n)	72 (50.7%)	100 (83.3%)	<0.001*
Age (years)	42.7 $\pm$15.6	52.0 $\pm$16.2	<0.001
Smokers (n)	22 (15.7%)	12 (10.0%)	0.199*
Basal FEV_1 (l)	84.9 $\pm$19.3	80.8 $\pm$18.4	0.060
Severity of illness			
Mild	94 (66.2%)	72 (60.0%)	0.403*
Moderate	28 (19.7%)	32 (26.7%)	
Severe	20 (14.1%)	16 (13.3%)	
Respiratory signs			
Age of onset (y)	28.2 $\pm$17.4	44.5 $\pm$17.4	<0.001
Duration (y)	14.5 $\pm$11.7	7.5 $\pm$10.7	<0.001
Digestive signs			
Age of onset (y)	—	36.6 $\pm$14.8	
Duration (y)	—	15.4 $\pm$11.0	
Clinical tests (n)	7.1 $\pm$6.9	12.0 $\pm$10.4	<0.001
Visits to GP's office (n)	5.5 $\pm$2.7	12.8 $\pm$7.9	<0.001
Absenteeism (days)	6.7 $\pm$4.1	26.9 $\pm$21.0	<0.001
Hospitalisation			
Rate (n)	49 (34.5%)	112 (93.3%)	<0.001*
Duration (days)	17.8 $\pm$34.5	11.3 $\pm$10.0	0.829
Drug load (n)	1.7 $\pm$0.9	3.6 $\pm$1.6	<0.001

n, %, mean $\pm$SD; y, years.
*Fisher's exact test, Wilcoxon rank-sum test everywhere else.

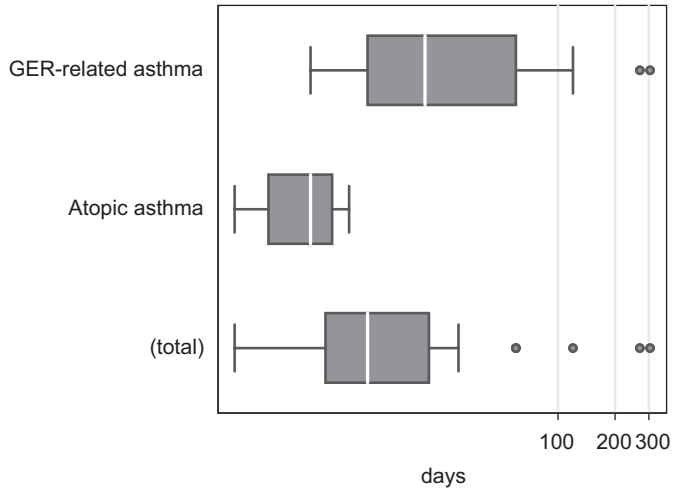

Figure 1 Absenteeism in the total sample of subjects, in atopic, and in GER-related asthmatics.

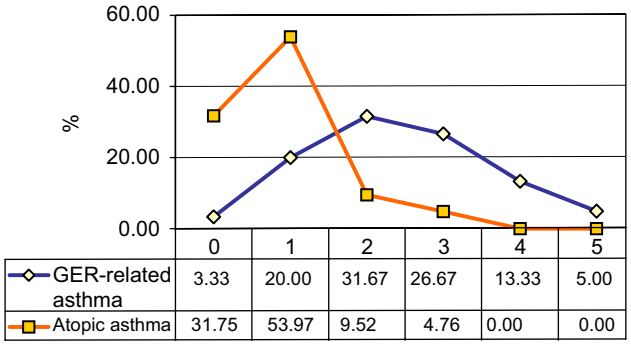

Figure 2 The therapeutic load and the frequency distribution of the number of drugs taken by atopic and GER-related asthmatics.

subjects: 5.5±2.7 SD in atopic and 12.8±7.9 SD in GER-related asthmatics ($p = 0.001$). Concerning absenteeism from work, the mean number of days off registered for GER-related asthmatics was significantly higher than that in atopic asthmatics: mean value = 26.9 days±21.0 SD and 6.07 days±4.1 SD, respectively ($p < 0.001$). The corresponding distributions of values are reported in Table 1 and Fig. 1.

While the mean duration of hospital stay was similar in the two subgroups of patients (both median value = 7), the hospitalisation rate proved quite different (93.3% vs. 34.5%, $p < 0.001$).

The therapeutic approach was different in the two groups of subjects. When considering the frequency distribution of the number of drugs taken by patients, it is clear that GER-related asthmatics usually had a higher therapeutic load (Fig. 2). In particular, only 31.8% of atopic subjects and 3.3% of GER-related asthmatics did not take a drug regularly, with the large majority of patients in the latter group being treated with more than two drugs concomitantly (Fig. 2).

The eight prevailing drugs for both groups (i.e. the "top eight") are reported analytically in Table 2. While long-acting β_2-adrenergics (LABA) and inhaled steroids (ICS) were the most frequently used therapeutic options (44.1%) in atopic asthmatics, digestive drugs (such as PPI, H_2 antagonists, pro-kinetics) were the most frequently used (22.7%) in GER-related asthmatics, together with anxiolytic drugs (9.9%). The use of short-acting β_2 adrenergics (SABA) was quite similar in both groups (19.5% vs. 18.2%, respectively),

Table 2 Therapeutic approach and the "top eight" drugs for treatment of atopic and GER-related asthma.

	%
Atopic asthma	
LABA+ICS	44.1
SABA	19.5
Systemic steroids	9.1
Anti-H_1/anti-LTs	7.8
Theophylline	7.3
Anti-tussive/mucoactive	4.8
Anxiolytic	3.3
Digestive	2.6
Prokinetic	1.9
PPI/anti-H_2	0.7
GER-related asthma	
Digestive	22.7
Prokinetic	16.1
Anti-H_2/PPI	6.6
Systemic steroids	15.8
SABA	18.2
Anxiolytic	9.9
anti-tussive/mucoactive	9.1
ICS	7.4
Theophylline	7.0
LABA+ICS	4.5

SABA: short-acting β_2 adrenergics; LABA: long-acting β_2 adrenergics; ICS: inhaled corticosteroids; anti-H_1: histamine receptor 1 antagonists; anti-LTs: leukotriene receptor antagonists; anti-H_2: histamine receptor 2 antagonists; PPI: proton pump inhibitors.

Table 3 Analytical and total median annual costs per patient (in Euro) calculated in atopic and GER-related asthma subjects (interquartile range (iqr), ratio of cost on total annual expenditure (%) and *p*-value of rank sum test in the two groups).

	Atopic asthma			GER-related asthma			*p*-value
	Median	iqr	%	Median	iqr	%	
Drug-induced	423.4	(604.4)	23.3	496.5	(860.1)	11.1	0.004
Medical visits	124.0	(82.6)	5.7	227.3	(247.9)	4.2	<0.001
Diagnostic tests	235.6	(194.8)	15.0	392.8	(336.6)	8.5	<0.001
Hospitalisation*	567.1	(±11.0)	45.5	2201.0	(±90.0)	55.5	<0.001
Day hospital*	24.7	(±12.6)	2.0	43.6	(±11.1)	1.1	<0.001
Absenteeism*	103.6	(±33.9)	8.3	748.7	(±94.7)	18.9	<0.001
Total cost**	1246.7	(1979.6)	100.0	3967.1	(3751.5)	100.0	<0.001

*Mean ± SD because median cost = 0.

**Median total cost calculated as the median of all costs distribution: for this reason, its value does not correspond to the simple sum of different median costs reported.

as well as that of theophylline (7.3% and 7.0%, respectively). The use of systemic steroids was much higher in GER-related asthmatics (15.8% vs. 9.1%). The consumption of other symptomatic drugs (such as anti-tussive and mucoactive drugs) was also higher in GER-related asthma subjects (9.1% vs. 4.8%).

The median annual costs per patient calculated in the two groups of subjects are reported analytically in Table 3, together with median and interquartile range values. The median overall drug-induced annual cost per patient was €423.4 (iqr 604.4) in atopic and €496.5 (iqr 860.1) in GER-related asthma subjects ($p = 0.04$). Per-patient costs induced by medical consultations (visits to GPs and lung physicians) and those due to diagnostic procedures were higher in GER-related asthmatics: €227.2 (iqr 247.9) vs. €124.0 (iqr 82.6) ($p<0.001$) and €392.8 (iqr 336.6) vs. 235.6 (iqr 194.8) ($p<0.001$), respectively. Per-patient direct costs due to hospital admissions were also higher in GER-related asthma subjects: 2201.7 ± 90.0 SD vs. €567.1 ± 11.0 SD ($p<0.001$). In particular, per-patient costs due to day-hospital activities were €43.6 ± 11.1 SD and €24.7 ± 12.6 SD ($p<0.001$). Annual indirect costs due to days off work were also higher in these subjects: €748.7 ± 94.7 SD vs. €103.6 ± 33.9 SD ($p<0.001$).

When compared to the corresponding total annual expenditure, drugs accounted for 23.3% of total costs in atopic and only 11.1% in GER-related asthma. The percent economic impact of hospital admissions was 45.5% in atopic and 55.5% in GER-related asthmatics, with absenteeism being 8.3% and 18.9%, respectively.

Discussion

Bronchial asthma is a costly disease which involves a high resource utilisation. The economic impact of bronchial asthma consists of direct medical expenditures (i.e. payments for ambulatory care visits; hospital out-patient services; hospital in-patient stays; visits to the emergency department; prescribed medicines and diagnostic tests) and indirect medical costs (i.e. missed work; restricted activities; loss of work opportunities).[1–4]

In addition, the most recent pharmaco-economic studies tend to emphasise that asthma is still receiving increasing attention,[5–8] and optimisation of the major outcomes is usually achieved by comparing the efficacy and the effectiveness of different therapeutic strategies, with good pharmacological control of asthma being the primary goal in these studies.[9,10] The best choice of current pharmaceutical options is generally regarded as the major opportunity to achieve the best asthma control, simply reflecting the actual value for money, even though the adequate diagnosis and classification of asthma is a crucial point.[11]

Nevertheless, health economic studies have not examined the different underlying aetiologic determinants of bronchial asthma, even though it has long been known that when the atopic origin of bronchial asthma is excluded, assessment of the precise origin of the disease can be very difficult, and the appropriate diagnosis can frequently take long time independently of the therapeutic strategies adopted. Achieving good value for money is mainly affected by the low specificity and long duration of the diagnostic procedures in these cases, rather than by the therapeutic approach to the disease, unless aetiologically oriented. In other words, the "diagnosis effect" should also play a crucial role in the overall cost-of-illness analysis of asthma.

The evidence concerning the triggering and/or the causative role of GER in asthma (particularly in non-atopic subjects) has been strongly emphasised in recent years also in clinical studies.[12–17] At present, GER-related asthma still represents a type of asthma where the onset, or the persistence, of specific digestive symptoms is only infrequently supported by corresponding significant changes in lung parameters (such as volume, flow, conventional bronchial hyper-responsiveness),[23–26] and the diagnostic pattern of asthma can then be difficult depicted in a short time.

All these findings contributed to the inclusion of GER-related asthma in the group of "difficult asthma". Although it has never been considered from this point of view, the clinical difficulties in assessing the true origin of this type of

asthma could be presumed to cause a notable growth in economic costs, which is mainly related to its delayed aetiologic diagnosis and consequently to its inappropriate clinical management.

To our knowledge, no controlled investigation has been published to date, and the present study can be regarded as the first pivotal study on this specific topic.

In general terms, data from the present study tend to indicate that GER-related asthma is much more costly than atopic asthma, despite the fact that the respiratory symptoms have a shorter mean duration (i.e. their onset occurs in later ages), and mainly affects subjects who report notable digestive symptoms that started long before. This particular information confirms previous studies which proved that asthma due to GER mainly occurs in older people than atopic asthma, and that females are more affected.[27]

The difficulty in defining the pathogenic relationship between the subject's complaint of both digestive and respiratory symptoms is likely reflected by the large number of clinical and instrumental tests required to clarify the cause of asthma in these cases. All these diagnostic procedures significantly affect total healthcare costs, both direct and indirect costs.

The higher level of absenteeism and the more frequent hospitalisations documented in this group of subjects can be likely explained by the persisting diagnostic uncertainty. Unfortunately, a longer delay in the aetiologic diagnosis of asthma is frequent when facing this kind of clinical problems, being the uncertainty in the diagnostic process also confirmed by the growing trend of heavier therapeutic loads systematically found in GER-related asthmatics (i.e. an average of three different drugs in 50% of subjects). Furthermore, the therapeutic approach to GER-related asthma proves frequently inadequate, being teophylline (such as a pro-refluxant drug), oral steroids and ansiolytics too widely used in these cases. These patients most likely prove to be unresponsive to conventional first-line asthma treatments, and further therapeutic options are continuously added in the attempt to achieve a better control of the disease.

Contrary to the clear therapeutic options generally registered in atopic asthma (which were in pretty good agreement with the international guidelines), the therapeutic approach to GER-related asthma usually reflects a persisting symptomatic approach to this digestive–respiratory disease, particularly intriguing.

In the present study, the mean absolute cost of drug consumption was higher than in previous healthcare investigations on asthma.[3,4] However, in the present study, mild, moderate and severe asthma were assessed according to the "during treatment" GINA classification; in these cases, the intrinsic severity of the disease[18] was more relevant and the mean patient drug requirement higher.

Because GER-related asthma frequently affects individual who are still active and productive, hospital in-patient stay, hospital out-patient services and absenteeism from productive activities actually represent the major categories of expenditure (66.1% mean total costs). It should also be emphasised that the long time required for diagnostic procedures and diagnostic conclusions can contribute towards increasing the direct and indirect costs. In our opinion, the difference in illness-associated costs between GER-related and atopic asthma proved too high to be suggested as solely dependent of the slight difference in distribution of asthma severity as observed in the two groups.

In conclusion, GER-induced asthma seems to cause a much higher economic impact than atopic asthma. Although further studies are needed, data from the present pivotal study tends to suggest that when facing difficult asthma, GER-related asthma in this case, stringent attention to the precise aetiological definition of the disease can play a critical role (i.e. a sort of "diagnosis effect") in limiting healthcare expenditures and in optimising the approach to patients' needs.

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