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Asthma-related resource use and cost by GINA classification of severity in three European countries

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Summary
Background: This study assessed the relationship between asthma burden and asthma severity in France, Italy, and Spain.
Methods: Adult asthmatics, 18–55 years of age, completed a questionnaire while visiting a respiratory physician in 1998 and 1999. Asthma severity was categorized by physicians as intermittent, mild persistent, moderate persistent, or severe persistent according to Global Initiative for Asthma (GINA) guidelines.
Results: Totals of 282 patients in France, 500 in Italy, and 296 in Spain entered the study. There were few differences between the three countries in the asthma symptom burden. Most patients with persistent asthma had used inhaled corticosteroids in the previous 14 days. Unexpectedly, 35% (Italy) to 83% (Spain) of patients with intermittent asthma also had used inhaled corticosteroids. In Spain, visits to the emergency department were more frequent (OR 7.0, 95% CI 4.9–10.0 with Italy as reference) and the costs of emergency care in all asthma severity categories were up to 10 times higher than in Italy and France. The frequency of hospitalizations did not differ systematically between the three countries.
Conclusions: Inadequate control of asthma symptoms among patients with severe persistent asthma could not be entirely explained by under-prescribing of asthma medications. The use of inhaled corticosteroids by patients with intermittent asthma might reflect misclassification of asthma severity, possibly due to difficulty in interpreting the GINA guidelines. The relatively high cost of emergency care in Spain

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does not appear to be related to greater asthma severity or poorer symptom control, but may be a feature of the Spanish health care system.

Introduction

The treatment recommendations for asthma in international guidelines depend on the underlying severity of the disease. In principle, asthma severity is determined most accurately by the patient's clinical condition in the absence of therapy. Appropriate therapy minimizes the symptom burden, so that the presence of residual symptoms and exacerbations in treated patients reflects lack of control: this defines the difference between severity and control.[1] The determination of underlying severity is thus important, not only in determining treatment, but also in assessing the effectiveness of the treatment and the societal costs of inadequate control, measured in terms of the symptom burden and the costs of emergency care.

Asthma severity has frequently been determined on the basis of symptoms in populations already being treated. But treatment confounds the assessment severity and control.[2–5] Furthermore, most studies of the asthma burden apply to a specific country and cannot be extrapolated to other countries, because of variations in health care systems, provider behavior, and patient characteristics. Here we report a study that compares the relationship between severity and the asthma burden in three major European countries. Severity was determined by taking into account the three dimensions of symptoms, lung function, and medication use, in accordance with the Global Initiative for Asthma (GINA) guidelines,[6–8] as a practical means of categorizing patients in populations already receiving treatment.[9] The objectives were, first, to evaluate asthma-related resource use in a selection of European countries according to asthma severity and, second, to compare variations in asthma-related resource use between the countries, using the same criteria for severity.

Methods

Study design and procedures

This study was a survey of consecutive adults with asthma, conducted during regularly scheduled visits to respiratory clinics (nine in France, 16 in Italy, and 52 in Spain) during 1998 and 1999. The participating physicians in France and Italy were allergists, pulmonologists, or internists experienced in asthma care and the clinics were a convenience sample in each country. In Spain, the participating physicians were family and community physicians (Medicina de Familia y Communitaria) providing continuous care for asthma and other respiratory diseases. Specialist centers, rather than general practices, were chosen to ensure a patient sample that included all degrees of asthma severity. The methods did not differ between countries and have been previously described in detail for the Italian arm of the study.[10]

In brief, patients were eligible if they were between 18 and 55 years of age and had at least a 1-year history of asthma. During the course of a routine office visit, patients recorded socio-demographic information, asthma symptoms in the previous 14 days, asthma medication use during past 14 days, physician visits during past 6 months, and hospitalization and emergency department visits during past year, using a self-administered questionnaire. Productivity loss in the past year was recorded as paid workday loss per month and decreased effectiveness at work. Physicians categorized the severity of the patient's asthma as intermittent, mild persistent, moderate persistent, or severe persistent, according to the 1995 GINA classification system,[11] based on a combination of symptom and FEV_1 criteria and the GINA recommendations for medication appropriate at each level of severity.[7] Asthma severity levels were determined for the past 14 days. For the cost analysis, units of resource consumption obtained from the questionnaires were extrapolated to a 1-year period without adjustment. Unit drug costs were taken from the official drug wholesale price lists in the respective countries, and costs of ambulatory visits, tests, and hospital admissions were based on the official tariffs of the respective national health services. Indirect costs were estimated as the asthma-related productivity loss multiplied by the average wage, obtained from national statistical institutes in each country. Costs were calculated in local currencies and converted to 1999 Euros. The total cost of asthma was the sum of the direct medical cost and the indirect cost.

Statistical analysis

The chi-square test (homogeneity of distribution) was used to assess associations between asthma severity and categorical variables. General linear models were used to assess the relationship between asthma severity and continuous variables. The non-parametric Kruskal–Wallis test was applied when the variable had a skewed distribution. Multivariable logistic regression models were constructed to determine the associations between asthma severity and asthma-related hospital admissions and emergency department visits. A two-tailed P value <0.05 was considered significant and all analyses were carried out using SAS software package (version 8.2).

Results

Patient population

One thousand and seventy-eight patients were included in the analysis: 282 in France, 500 in Italy, and 296 in Spain. Italy and Spain had similar distributions of asthma severity, with 35–44% of patients classified as having intermittent asthma and 4–8% classified as having severe persistent asthma (Table 1). Conversely, only 4% of patients in France had intermittent asthma, while 28% had severe persistent asthma. Female patients predominated, but there was no relationship between sex and asthma severity. The mean patient age increased statistically significantly with asthma severity in all three countries.

Asthma symptom burden

All categories of asthma symptoms reported by patients increased with asthma severity (Table 2). There was no striking difference between the three countries in the asthma symptom burden in each severity category, although the burden was higher in Italy in some instances—nights woken up in patients with severe persistent asthma; and impact of asthma exacerbations in patients with moderate and severe persistent asthma.

Asthma medications

Most but not all patients with persistent asthma had used inhaled corticosteroids in the 14 days prior to completing the questionnaire (Table 3). Unexpectedly, 35–83% of patients with intermittent asthma had also used inhaled corticosteroids. There was less use of inhaled corticosteroids in Italy than in the other two countries.

Asthma-related medical service use

The use of all categories of medical services tended to increase with asthma severity (Table 4). Italy and Spain were similar in terms of the numbers of patient-reported GP visits, which for patients in the intermittent, mild-, and moderate persistent categories were approximately 2–4 times more frequent than in France. In other categories of medical service use, however, Spain was distinct from the other two countries: in Spain, visits to specialist physicians were less frequent and visits to the emergency department were more frequent than in

Table 1 Patient characteristics by asthma severity and country.

	Asthma severity				P value
	Intermittent	Mild persistent	Moderate persistent	Severe persistent	
Patient number (%)					
France ($N = 282$)	12 (4%)	88 (31%)	102 (36%)	80 (28%)	—
Italy ($N = 500$)	174 (35%)	134 (27%)	153 (31%)	39 (8%)	—
Spain ($N = 296$)	131 (44%)	85 (29%)	69 (23%)	11 (4%)	—
Female (%)					
France	54.6	62.5	59.8	57.5	NS
Italy	56.3	53.7	56.9	74.4	NS
Spain	67.7	76.5	69.6	90.9	NS
Age, mean years (SD)					
France	37.2 (9.9)	35.0 (11.8)	39.3 (10.5)	41.0 (10.7)	0.0034
Italy	34.2 (9.8)	36.0 (10.5)	38.5 (10.8)	42.0 (11.6)	<0.0001
Spain	35.0 (11.3)	39.2 (11.5)	39.1 (11.4)	47.5 (9.6)	0.0005

Table 2 Patient-reported symptoms during the previous 14 days by asthma severity and country.

	Asthma severity				*P* value
	Intermittent	Mild persistent	Moderate persistent	Severe persistent	
Mean days with symptoms (SD)					
France	1.9 (3.9)	3.2 (4.8)	4.2 (4.9)	8.8 (5.8)	<0.0001
Italy	1.1 (1.9)	4.3 (4.4)	6.4 (5.0)	9.3 (5.3)	<0.0001
Spain	1.5 (3.0)	3.4 (4.2)	7.5 (5.6)	8.4 (6.1)	<0.0001
Mean nights woke up (SD)					
France	0.9 (2.9)	1.0 (2.8)	1.2 (2.4)	4.4 (5.5)	<0.0001
Italy	0.2 (0.7)	1.3 (2.1)	3.1 (4.0)	7.2 (5.8)	<0.0001
Spain	0.5 (1.9)	0.7 (1.5)	2.8 (4.1)	3.5 (4.7)	<0.0001
Moderately or severely limited in normal daily activities (%)*					
France	0	8.0	19.6	57.5	<0.0001
Italy	0	1.5	26.8	59.0	<0.0001
Spain	1.5	3.5	20.3	54.6	<0.0001
Moderate or major impact of asthma exacerbations† (%)					
France	0	8.0	11.8	38.8	<0.0001
Italy	0	3.7	26.8	66.7	<0.0001
Spain	2.3	3.5	11.6	45.5	<0.0001

*Limited most or all of the time.
†Impact on sleep and activities most or all of the time.

Table 3 Patient-reported medication use during the past 14 days by asthma severity and country.

	Asthma severity				*P* value
	Intermittent	Mild persistent	Moderate persistent	Severe persistent	
Short-acting beta-agonists (%)					
France	75.0	65.9	71.6	82.5	NS
Italy	35.1	81.5	64.1	79.5	<0.0001
Spain	61.1	81.2	78.3	81.8	0.0045
Inhaled corticosteroids (%)					
France	83.3	80.7	93.1	95.0	0.0087
Italy	35.1	66.4	75.2	64.1	<0.0001
Spain	71.8	88.2	89.9	100.0	0.0008
Long-acting beta-agonists (%)					
France	58.3	44.3	65.7	77.5	0.0001
Italy	25.3	53.0	64.7	51.3	<0.0001
Spain	28.2	31.8	55.1	72.7	0.0001
Oral corticosteroids (%)					
France	0	8.0	7.8	42.5	<0.0001
Italy	4.0	5.2	15.7	33.3	<0.0001
Spain	3.8	1.2	5.8	27.3	0.001

Italy and France. Hospitalizations did not differ systematically across these three countries, but instead correlated with asthma severity. In all countries, the difference between severe persistent and other severity categories in hospitalization rates was dramatic.

Predictors of emergency care

In multivariable logistic models, patients in Spain were more likely to visit the emergency department than patients in Italy (odds ratio [OR] 7.0, 95% confidence interval [CI] 4.9–10.0), while patients in

Table 4 Patient reported asthma-related medical service use during the past year by severity and country.

	Asthma severity				*P* value
	Intermittent	Mild persistent	Moderate persistent	Severe persistent	
GP visits, mean number (SD)					
France	1.3 (2.7)	1.8 (3.6)	2.1 (2.9)	7.7 (10.6)	<0.0001
Italy	3.1 (5.7)	4.8 (8.6)	6.2 (12.6)	8.6 (12.0)	0.0019
Spain	4.2 (4.3)	6.4 (5.6)	7.8 (6.7)	10.0 (4.9)	<0.0001
Specialist visits, mean number (SD)					
France	3.2 (1.6)	3.2 (2.4)	4.1 (4.6)	6.9 (6.3)	<0.0001
Italy	3.5 (3.7)	4.5 (5.5)	4.3 (6.4)	4.7 (4.5)	NS
Spain	0.9 (1.6)	1.1 (2.2)	1.4 (2.3)	2.5 (5.9)	NS
Emergency department visits (%)					
France	8.3	13.6	6.9	25.0	0.0057
Italy	6.3	14.9	21.6	38.5	<0.0001
Spain	46.6	48.2	65.2	72.7	0.0329
Hospitalizations (%)					
France	8.3	8.0	9.8	38.8	<0.0001
Italy	3.5	6.7	8.5	33.3	<0.0001
Spain	5.3	5.9	7.3	27.3	0.0483

France were least likely to visit the emergency department (OR 0.6, 95% CI 0.4–0.9, with Italy as reference). The likelihood of an emergency department visit also increased with asthma severity. Patients with mild- (OR 1.6, 95% CI 1.1–2.5), moderate- (OR 2.3, 95% CI 1.5–3.6), or severe-persistent asthma (OR 5.6, 95% CI 3.2–9.9) were more likely to visit the emergency department than patients with intermittent asthma.

Multivariable logistic models revealed no significant difference between the countries in the likelihood of a hospital visit over a 1-year period, while patients with severe asthma were more likely to be hospitalized than patients with intermittent disease regardless of the country (OR 10.4, 95% CI 5.2–21.9).

Cost of asthma

The per-patient costs of asthma increased with increasing asthma severity (Table 5). Drug costs were lower in Italy than in the other two countries. The costs of emergency care were highest in Spain in all severity categories: 7 times higher than in France in the moderate persistent category and almost 10 times higher than in Italy in the severe persistent category. Direct costs exceeded indirect costs in France and Spain, but in Italy direct and indirect costs were comparable.

Discussion

This study applied a uniform methodology to the determination of asthma severity in 1078 adults attending clinics in France, Italy, and Spain. In all three countries the level of symptom control was poor among patients in the moderate and severe persistent asthma categories. Poor asthma control has been reported in population-based surveys of European countries, though the relationship with severity has not been previously clarified.[2,4,12–14] Poor asthma symptom control may be due in part to under-use of asthma controller medications. Not all patients with persistent asthma were using inhaled anti-inflammatory drugs, particularly in Italy, where inhaled corticosteroid use was lower, while the symptom burden was by some measures higher, than in France or Spain.

It seems unlikely, however, that the poor symptom control can be entirely explained by under-prescribing of asthma medications. Currently available medications do not achieve complete control of asthma in all patients even in the context of clinical trials.[15] Furthermore, virtually all patients ($\geqslant$99%) with persistent asthma in this study reported the use of one or more asthma medications in the previous 14 days. Most patients ($\geqslant$90%) with moderate or severe persistent asthma in France and Spain reported use of inhaled corticosteroids. The ratio of inhaled corticosteroid to short-acting beta-agonist use was approximately unity in

Table 5 Per-patient cost of asthma in euros by asthma severity and country*.

	Asthma severity				*P* value
	Intermittent	Mild persistent	Moderate persistent	Severe persistent	
ED and hospitalization					
France	180 (620)	220 (800)	250 (800)	290 (260)	<0.0001
Italy	66 (340)	300 (1900)	240 (1100)	890 (1400)	0.002
Spain	210 (450)	340 (690)	1800 (11,000)	8600 (27,000)	0.0019
Physician visits					
France	96 (56)	110 (99)	130 (120)	290 (260)	<0.0001
Italy	110 (110)	150 (180)	170 (220)	210 (170)	0.0031
Spain	110 (130)	150 (190)	180 (200)	250 (320)	0.0081
Asthma-related drugs					
France	560 (460)	490 (700)	810 (470)	1400 (900)	<0.0001
Italy	120 (630)	93 (260)	350 (1200)	400 (1300)	0.0166
Spain	330 (850)	540 (1100)	520 (980)	1300 (1800)	0.0187
Direct medical cost					
France	840 (1000)	820 (1100)	1200 (1000)	3300 (3000)	<0.0001
Italy	300 (730)	550 (2000)	760 (1700)	1500 (2200)	0.0002
Spain	650 (1100)	1000 (1600)	2500 (11,000)	10,000 (27,000)	0.0004
Indirect cost					
France	0	95 (370)	60 (260)	880 (2700)	0.0009
Italy	420 (1300)	500 (1300)	780 (2100)	1800 (3900)	0.0003
Spain	180 (900)	180 (700)	250 (790)	16 (54)	NS
Total cost					
France	840 (1000)	910 (1300)	1300 (1100)	4100 (4300)	<0.0001
Italy	720 (1500)	1000 (2500)	1500 (2700)	3300 (4900)	0.0001
Spain	830 (1500)	1200 (1900)	2700 (11,000)	10,000 (27,000)	0.0006

*Values represent mean (SD) asthma-related cost, given to two significant figures.

all three countries. This contrasts with previous reports from population-based studies in France, Italy, and Spain, where the ratio of inhaled corticosteroids to quick-relief medications was <0.35.[2,16]

Neither poor symptom control nor under-use of asthma drugs appear to explain the extremely high rate of emergency department visits in Spain (between 47% and 73% of patients, depending on severity). The asthma symptom burden in Spain was comparable to that in France and Italy. Similarly, the use of inhaled corticosteroids and short-acting beta-agonists was as great or greater in Spain than in France or Italy. A high rate of emergency care visits in Spain was noted in the population-based AIRE study and in the European Community Respiratory Health Survey.[3,16] In the AIRE survey, 22% of adults with asthma visited the emergency department in the previous year in Spain, compared with 5% in France and 11% in Italy.[16] This difference could not be attributed to a difference in asthma medication compliance.[3] A concomitantly low frequency of specialist visits in Spain suggests that the high frequency of emergency department visits is a feature of the health care system: patients in Spain may use the emergency department for routine visits and not just for emergency care. A study of hospital emergency services use in Barcelona indicated that only 38% of cases were actual emergencies.[17] The factors invoked to explain this were related to demand (an ageing population, a 'hospital-centric' culture, health education) and supply (lack of accessible primary care facilities, greater accessibility of hospitals), although these factors do not entirely explain the phenomenon.[17]

As the classification of asthma severity according to GINA criteria has not been validated against a 'gold standard' (e.g., determination of severity based on symptoms in the absence of drug treatment), the categorizations may have been inaccurate. Differences between countries in physician specialty might also have contributed to differences in severity classification. The investigators in

France (where 4% of patient were classified as having intermittent asthma) were respiratory specialists, whereas those in Spain (where 44% of patients were in the intermittent category) were family and community physicians. The surprising finding, that from 35.1% (Italy) to 83.3% (France) of patients with intermittent asthma had used inhaled corticosteroids in the previous 14 days, might be explained by misclassification of asthma severity. That is, it is possible that the control of asthma symptoms resulting from the use of inhaled corticosteroids was confounded with the absence of persistent asthma. This might indicate the difficulty in applying GINA guidelines to determining asthma severity in clinical practice. The limited data available indicate that the inter-rater reliability of severity classification using the guidelines is poor, though treatment recommendations are consistent with physicians' severity classifications.[18] The use of inhaled corticosteroids by patients in the intermittent category might nevertheless reflect mis-prescribing of asthma medications. The asthma medications that patients reported taking in the previous 14 days had been prescribed in an earlier visit to a GP or other physician, who then referred the patient to the investigating physician. That is, the referring physician rather than the investigating respiratory physician may have misdiagnosed the severity of the patients' asthma. This argument is applicable to Italy and Spain, but less so to France, where relatively few patients (4%) were in the intermittent asthma category. In France it is more likely that, as allowed in the GINA guidelines, patients with intermittent asthma were prescribed a short course of inhaled corticosteroids to treat a transient episode of severe symptom exacerbation.[6]

Limitations in the study design affect the interpretability of the results. We limited the study to patients seen by respiratory physicians. Because of this and other patient selection criteria, the patients were not nationally representative samples and our observations might not be generalizable to all people with asthma in the three countries studied. A study carried out in Italy in 1998–2000 indicated that only 57.4% of young adults with asthma had been seen by a doctor in the previous 12 months, but that almost two-thirds of those who (62.5%) had been seen by a specialist.[4] The recall periods specified in the study questionnaire were chosen to maximize the accuracy of self-reported data for events of differing frequencies: a 14-day recall period for common events (asthma symptoms and medication use) and 6- and 12-month recall periods for less frequent events (emergency care). While a short recall period might accurately reflect the actual events,[19] there is uncertainty in extrapolating to longer time frames.

Conclusions

A GINA-based severity classification system that took into account symptoms, lung function, and medication use, was applied in an attempt to distinguish between asthma severity and control. Incomplete control of asthma, particularly among patients with moderate and severe persistent asthma, occurred at comparable rates in France, Italy, and Spain, and could only partly be explained by under-prescription of asthma medications. Similar rates of hospitalization in the three countries suggest relative homogeneity in admission policies. The reasons for a high frequency of emergency department visits in Spain require further study.

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