

Direct Costs of Acute Rhinosinusitis in Spain: A Prospective and Observational Study (PROSINUS)

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■ Abstract

Background: The incidence of acute rhinosinusitis (ARS) is high throughout the world. Although diagnosis is clinical and disease course is mostly self-limiting, diagnostic tools and medications are overused by physicians, thus increasing the direct medical costs of the disease.

Objective: The aim of the PROSINUS study was to quantify the direct medical costs of management of ARS in Spain.

Methods: We performed a prospective observational study of 1610 patients with a clinical diagnosis of nonbacterial, uncomplicated ARS. According to the duration of symptoms by the European Position Paper on Rhinosinusitis and Nasal Polyps, patients were classified as having viral or postviral ARS with different levels of severity. Direct medical costs were calculated based on medical visits, use of diagnostic tools, and medications prescribed.

Results: Overall, the mean (SD) direct medical costs per episode were €322.3 (301.2) vs €441.1 (344.3) for viral and postviral ARS episodes, respectively ($P < .001$). When viral and postviral disease were compared, the medical costs per episode were €245.0 (265.4) vs €328.4 (301.9) for medical visits ($P < .001$), €38.1 (64.0) vs €61.9 (78.8) for diagnostic tools ($P < .001$), and €39.2 (25.9) vs €50.8 (25.3) for medications prescribed ($P < .001$).

Conclusions: The direct medical costs of postviral ARS episodes were higher than those of viral episodes (common cold). Uncomplicated nonbacterial ARS represents an important socioeconomic burden owing to the excessive number of medical visits, use of diagnostic tools, and medications prescribed.

Key words: Acute rhinosinusitis. Common cold. EPOS. Direct costs. PROSINUS.

■ Resumen

Antecedentes: La rinosinusitis aguda (RSA) tiene una alta incidencia en la población general. Aunque el diagnóstico es clínico y la evolución es principalmente autolimitada, existe un uso excesivo de herramientas diagnósticas y medicamentos por parte de los médicos, lo que aumenta los costes médicos directos de la enfermedad.

Objetivo: El objetivo del estudio PROSINUS fue cuantificar los costes médicos directos del manejo de la RSA en España.

Métodos: En un estudio observacional prospectivo, se incluyeron 1.610 pacientes con diagnóstico clínico de RSA no bacteriana y no complicada en España. De acuerdo con la duración de los síntomas según EPOS, los pacientes con RSA se clasificaron como RSA viral o posviral en función de los diferentes niveles de gravedad. Los costes médicos directos se calcularon según las visitas médicas realizadas, el uso de herramientas diagnósticas y los medicamentos recetados.

Resultados: En general, los costes médicos directos por episodio fueron de 322,3€ ± 301,2€ y de 441,1€ ± 344,3€ para los episodios de RSA viral y posviral respectivamente ($p < 0,001$). Al comparar viral versus posviral, los costes médicos por episodio de RSA fueron de 245,0€ ± 265,4€ vs. 328,4€ ± 301,9€ ($p < 0,001$) para las visitas médicas, de 38,1€ ± 64,0€ vs. 61,9€ ± 78,8€ ($p < 0,001$) para las herramientas diagnósticas, y de 39,2€ ± 25,9€ vs. 50,8€ ± 25,3€ ($p < 0,001$) para los medicamentos recetados.

Conclusiones: Los costes médicos directos de los episodios de RSA posviral fueron más altos que los virales (resfriado común). La RSA no bacteriana no complicada representa una carga socioeconómica importante debido a un número excesivo de visitas médicas, de herramientas diagnósticas y de medicamentos recetados.

Palabras clave: Rinosinusitis aguda. Resfriado común. EPOS. Costes directos. PROSINUS.

Introduction

Acute rhinosinusitis (ARS) is an inflammatory process that affects the paranasal sinuses and causes sinonasal symptoms lasting for <12 weeks [1]. ARS is caused mainly by viral infection/upper respiratory tract infection, although associated processes such as allergic rhinitis and smoking may act as predisposing factors [1-3]. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [1] defines ARS as a “sudden upset of two or more sinonasal symptoms, one of them being either nasal congestion/obstruction/blockage or nasal discharge (anterior or postnasal drip), and/or facial pain/pressure or reduction/loss of smell”.

EPOS classifies ARS as viral (common cold, upper respiratory tract infection), postviral, and bacterial, suggesting that they progress as a continuum [1]. Viral infection (common cold) accounts for most ARS cases [4,5], with a duration of up to 7-10 days. The disease is usually self-limiting. ARS is considered postviral when symptoms last more than 10 days or worsen after 5 days. Only a small percentage of the latter (0.5%-2%) progress to acute bacterial rhinosinusitis [6], which should be clinically suspected when patients present 3 out of the following 5 criteria: fever >38°C, severe unilateral pain, unilateral purulent rhinorrhea, worsening after initial recovery, and elevated erythrocyte sedimentation rate/C-reactive protein values [1,7,8]. Chronic rhinosinusitis (CRS) is clinically defined as rhinosinusitis in which symptoms persist without resolution for >12 weeks [1].

The incidence of viral ARS (common cold) is estimated to be 2-5 episodes per person per year [9], with that of postviral ARS being about 3-4 per 100 inhabitants per year [10]. The diagnosis of ARS is based on the clinical history and supported by examination of the ear, nose, and throat (ENT). Microbiology and imaging studies are not recommended in uncomplicated cases [1,11-13]. The treatment for ARS recommended by EPOS is based on symptomatic relief in mild/viral cases (analgesics, saline solution, short courses of nasal decongestants, and phytotherapy), intranasal corticosteroids in moderate/postviral cases, and intranasal corticosteroids plus oral antibiotics in severe/bacterial cases. Short courses (3 days) of oral corticosteroids are also recommended when severe unilateral facial pain is present [1,14,15]. There is no scientific evidence to recommend mucolytics or antihistamines for ARS, except in the case of allergic patients [1]. Although ARS is usually self-limiting and considered a low-risk disease, considerable economic resources are devoted to its management, thus creating a heavy burden for public health [2,16-20].

The PROSINUS study (PROspective epidemiological study about the diagnosis and therapeutic management of Acute RhinoSINUSitis in otorhinolaryngology clinics in Spain) analyses different aspects of treating ARS in Spain. The results are published in 2 manuscripts. In a recent publication [21], we reported overuse of diagnostic tools and medications prescribed by primary care physicians and ENT specialist in nonbacterial and uncomplicated ARS. Based on the EPOS recommendations, we identified a clear overuse of diagnostic tools, especially plain radiograph (64% of patients), and medications prescribed (71% antibiotics, 56% mucolytics, and 41% antihistamines).

The aim of the present study, the second manuscript resulting from the PROSINUS study, was to quantify the direct medical costs of nonbacterial uncomplicated ARS in Spain. We assessed health care burden according to medical visits, diagnostic tools used, and medications prescribed.

Material and Methods

Study Population and Design

We performed an epidemiological, prospective, real-life, descriptive study of a cohort of patients (N=2610) with acute nonbacterial, uncomplicated ARS in Spain. Patients were classified following the EPOS clinical diagnosis criteria as having viral ARS (common cold, duration <10 days) or postviral ARS (duration ≥10 days and <12 weeks). ENT specialists (N=284) from throughout Spain participated in the study. Each specialist included a mean (SD) of 9.1 (1.8) patients (range, 1-11).

Inclusion criteria: The study population comprised patients of both sexes aged ≥18 years who visited the ENT clinic with ARS symptoms according to the EPOS Consensus, namely, “acute onset of two or more sinonasal symptoms, one of which should be either nasal congestion/obstruction/blockage or nasal discharge/postnasal drip, as well as facial pain/pressure and/or reduction/loss of smell”.

Exclusion criteria: We excluded patients already diagnosed with chronic rhinosinusitis (CRS) who experienced an exacerbation, patients with ≥3 criteria for acute bacterial rhinosinusitis according to EPOS, and patients who were not able to attend follow-up visits or had a high risk of dropout.

Patients attended 2 visits, Visit 1 at inclusion and Visit 2 after 2-4 weeks. The items recorded at Visit 1 were diagnostic tools used and medications prescribed (by general practitioners), as well as the number of medical visits (scheduled visits to primary and secondary care and emergency visits) before the inclusion date. All patients had symptoms at Visit 1. The items recorded at Visit 2 were duration of the episode (in days), when the episode resolved, and classification as viral or postviral ARS. We also recorded diagnostic tools used and medications prescribed (by ENT specialists) between Visits 1 and 2, as well as the number of medical visits between Visit 1 and Visit 2. If the episode had not resolved at Visit 2, patients attended a third visit to establish the exact duration of the episode and were classified as having postviral ARS (up to 12 weeks) or CRS (more than 12 weeks).

The Ethics Committee of our institution (Hospital Clínic, Barcelona, Spain) approved the study, and all patients provided their signed informed consent.

Outcomes

Demographic characteristics, such as age and sex, were recorded at Visit 1. Disease severity was recorded using a visual analog scale (VAS, 0-10 cm), with patients classified as having mild ARS (VAS 0-3 cm), moderate ARS (VAS >3-7 cm), or severe ARS (VAS >7-10 cm). The duration of the episode (in days) using EPOS criteria was also recorded, with patients classified as having viral ARS (≤10 days) or postviral ARS

(>10 days). A number of additional outcomes were assessed and reported in our previous publication [21].

Diagnostic tools: Rhinoscopy and nasal endoscopy were considered as being included in the medical visit with no additional cost. At Visit 1 (before inclusion) and at Visit 2 (during the study), the use of different diagnostic tests (sinus x-ray, sinus computed tomography [CT], bacterial culture, anterior rhinomanometry, acoustic rhinometry, peak nasal inspiratory flow, subjective olfactometry [Barcelona Smell Test – 24 Odors]), and skin prick test results were also recorded. The unit cost of each diagnostic test was obtained from the cost database of Hospital Clinic de Barcelona (2017 Rate Cost), the total cost of diagnostic tests per episode being calculated accordingly.

Medications prescribed: The medications prescribed (nasal corticosteroids, nasal saline irrigation, phytotherapy, antibiotics, nasal decongestants, antihistamines, and mucolytics) and over-the-counter medications were recorded at Visit 1 and Visit 2. For the cost analysis, it was assumed that a patient would consume only 1 pack of each type of drug per episode. The unit cost of each medication was obtained from the Medicine Database of the General Council of the Spanish Official College of Pharmacists [22], the total cost of medications prescribed per episode being calculated accordingly. We also performed a comparison between the cost of correct and incorrect treatment, following the EPOS consensus, considering correct treatment for viral ARS to be nasal decongestants, nasal saline and/or phytotherapy, and, potentially, antihistamines (for allergic rhinitis), while antibiotics and nasal corticosteroids are not recommended. For postviral ARS, the treatments considered correct were nasal corticosteroids and, eventually, nasal decongestants, nasal saline, phytotherapy, and/or antihistamines (for allergic rhinitis). Since the disease studied was nonbacterial uncomplicated postviral ARS, antibiotics are not recommended.

Medical visits (scheduled with the primary care physician or ENT specialist and emergency visits) were also recorded during the ARS episode, while “study visits” were excluded from the costs. The unit cost of each visit was obtained from the database of the Hospital Clinic de Barcelona (2017 Rate Cost), the total cost of visits per episode being calculated accordingly.

Only direct medical costs were included in this analysis. Other direct costs, such as transport to the office, and indirect costs (absenteeism and presenteeism) were not assessed owing to the low number of patients reporting data. Unit costs (in euros) applied to specific health care resources (medical visits, diagnostic tools, and medications prescribed) are reported in Table 1.

Extrapolated outcomes: Given that Spain has a population of 46.7 million inhabitants [23], and according to epidemiological data (considering 2 viral episodes per person and year and 3 postviral episodes per 100 inhabitants per year), more than 90 million episodes of viral ARS (common cold) and 1.4 million episodes of postviral ARS are recorded each year. To extrapolate the results of the PROSINUS study to the total cost of ARS in the Spanish Health System, we considered different percentages of ARS patients consulting with their doctor: 3 for viral ARS (10%, 25%, and 33%) and 2 for postviral ARS (50% and 100%).

Table 1. Direct Costs of Acute Rhinosinusitis Used in the PROSINUS Study Analysis

Items	Cost, €
Visits to the doctor (per visit) ^a	
Emergency visit	223.00
Outpatient visit	137.00
Diagnostic tests (per procedure)	
Sinus x-ray	23.00
Sinus computed tomography scan	127.00
Microbiological culture	23.00
Anterior rhinomanometry	90.00
Acoustic rhinometry	16.00
Peak nasal inspiratory flow	16.00
Olfactometry (BAST-24)	227.00
Skin prick test	35.00
Drug therapy (per package) ^b	
Antibiotic	16.30
Intranasal corticosteroid	14.59
Oral H ₁ antihistamine	9.48
Nasal decongestant	4.56
Mucolytic	4.31
Saline solution	2.20
Phytotherapy	26.00

Abbreviation: BAST-24, Barcelona Smell Test–24 Odors.

^aHospital Clínic Barcelona rate cost 2017

^bBOTPLUS 2011

Statistical Analysis

The costs of medical visits, diagnostic tests, and drugs were calculated from onset to the end of the ARS event for each patient. The cost of drugs was calculated taking into account the unit cost per pack and the dose required.

A descriptive analysis was performed, with values expressed as mean (SD) or percentages, as appropriate. The *t* test and χ^2 test were used to compare continuous and categorical data, respectively, between the viral and postviral ARS groups. *P* values <.05 were considered statistically significant. All statistical analyses were performed using Stata version 15.

Results

Sociodemographic Characteristics

Of the initial 1678 patients included at Visit 1, 1362 were considered eligible for the study (Figure 1). Patients were classified into 3 groups according to the duration of symptoms: 36% (n=494) had common cold/viral ARS, 63% (n=857) had postviral ARS, and only 1% (n=11) had CRS. Patients with CRS were excluded from this analysis; therefore, the final sample size for the cost analysis was 1351 patients.

More women (53%) than men (47%) participated in the PROSINUS study, with a similar ratio in terms of viral and postviral ARS. According to the VAS score, few patients presented with mild ARS, and a similar proportion of patients presented with moderate or severe ARS. The participants' educational level was also similar in both groups (Table 2).

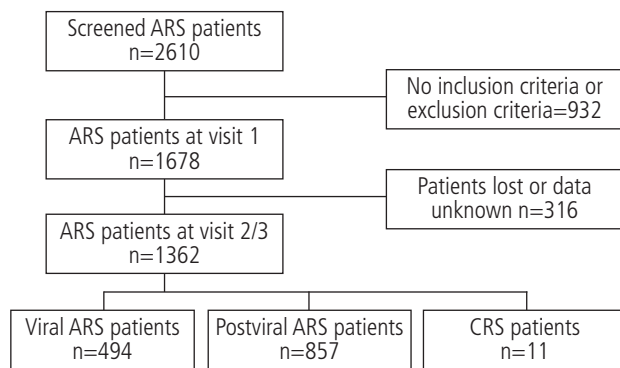


Figure 1. Flow-chart of participants in the PROSINUS study. Three rhinosinusitis phenotypes were obtained: viral ARS (common cold, 36%), postviral ARS (63%), and chronic rhinosinusitis (1%). ARS indicates acute rhinosinusitis. Figure modified from reference 18.

Table 2. Characteristics of Acute Rhinosinusitis (ARS) Patients Included in the PROSINUS Study

	Viral ARS (n=494)	Postviral ARS (n=857)	<i>P</i> Value
Mean (SD) age, y	42.2 (14.3)	42.6 (14.1)	.6871 ^a
Sex, No. (%)			
Male	234 (47)	375 (44)	.3534 ^b
Female	237 (48)	446 (52)	
Unknown	23 (5)	36 (4)	
Severity, No. (%)			
Mild	17 (3)	9 (1)	.0133 ^b
Moderate	254 (51)	432 (50)	
Severe	214 (43)	404 (47)	
Unknown	9 (2)	12 (1)	
Educational level, No. (%)			
Without/incomplete	45 (9)	84 (10)	.1842 ^b
Primary/secondary	219 (44)	415 (48)	
University/upper grades	225 (46)	355 (41)	
Unknown	5 (1)	3 (0)	

^at test (unpaired)

^bχ² test

Patient characteristics were fully described in our previous publication [21].

Cost Analysis

The overall direct costs for medical visits, diagnostic tools, and medications prescribed per episode and patient were higher in postviral ARS (€441.1 [344.3], $P < .001$) than in viral ARS (€322.3 [301.2]). Regarding viral ARS, the direct costs of severe episodes were higher (€386.1 [327.7], $P < .0001$) than those of moderate ARS (€275.3 [274.7]) and mild ARS (€220.4 [167.2]). Regarding postviral ARS, the direct costs of severe episodes were also higher (€499.5 [382.6], $P < .0001$) than those of moderate episodes (€384.5 [290.4]) and mild episodes (€310.5 [242.6]). The difference between mild disease (€220.34 [167.2] for viral; €310.5 [242.6] for postviral) and

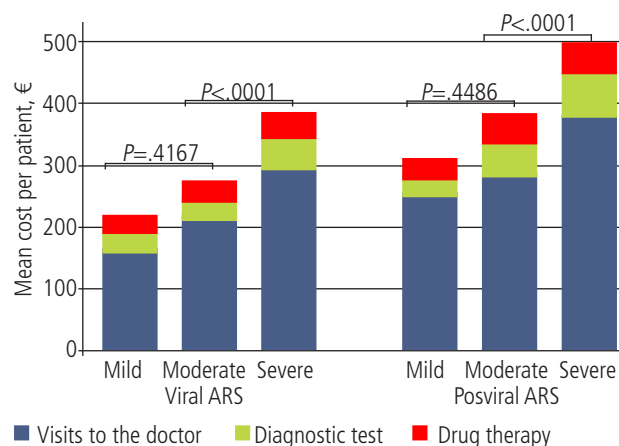


Figure 2. Direct costs of ARS according to disease duration and severity. Bars represent the cost (in euros) per ARS episode and patient in each level of severity for both viral ARS (common cold) and postviral ARS. ARS indicates acute rhinosinusitis.

moderate disease was not statistically significant in either the viral or the postviral group (Figure 2).

Medical visits: Besides the study visits, almost all patients (82%) attended at least 1 additional medical visit. Approximately 1 out of 4 patients with viral ARS and postviral ARS attended an emergency visit, with no difference between the groups (24% and 26%, respectively). More postviral than viral ARS patients also attended a scheduled visit with the ENT specialist (48% vs 35%, $P < .001$) or with the primary care physician (60% vs 48%, $P < .001$) (summarized from reference 21). The medical visits were the item with the highest associated cost, at €245.0 (265.4) and €328.4 (301.9) for viral and postviral ARS, respectively ($P < .001$) (Table 3). Concerning severity, the direct costs related to medical visits for severe postviral ARS were higher (€377.5 [340.4]) than for moderate disease (€270.5 [247.6]) and mild disease (€251.3 [197.5]) ($P < .0001$). The difference between severity groups regarding viral ARS episodes was also significant (€157.2 [135.8] for mild disease, €210.8 [251.7] for moderate disease, and €292.3 [281.6] for severe disease; $P < .0014$) (Figure 2, in blue).

Diagnostic tools: The most frequently diagnostic tools used were anterior rhinoscopy/nasal endoscopy (76%), x-ray (64%), CT scan (18%), and microbiology cultures (7%), all of which were performed more frequently ($P < .002$) in postviral ARS than in viral ARS (summarized from reference 21). The costs of the diagnostic tools used were significantly higher in postviral ARS (€61.7 [78.8]) than in viral ARS (€38.1 [64.0]) ($P < .001$) (Table 3). The direct costs related to diagnostic tools for viral ARS were €31.9 (51.1) for mild episodes, €28.5 (48.3) for moderate episodes, and €49.6 (79.2) for severe episodes ($P < .0018$). For postviral ARS, the costs were €25.7 (60.6) for mild episodes, €50.6 (72.4) for moderate episodes, and €69.5 (85.2) for severe episodes ($P < .0152$) (Figure 2, in green).

Medications prescribed: All medications, except phytotherapy, were more frequently prescribed ($P < .05$) in postviral ARS than in viral ARS as follows: oral antibiotics

Table 3. Direct Costs of ARS According to Disease Duration

	Viral ARS (n=494)		Postviral ARS (n=857)		P Value ^c
	Counts ^a	Cost, € ^b	Counts ^a	Cost, € ^b	
Visits to the doctor, mean (SD)					
Emergency visits	0.30 (0.67)	67.3 (148.3)	0.33 (0.62)	73.38 (138.3)	.4459
Outpatient visits	1.30 (1.55)	177.8 (212.4)	1.86 (1.90)	254.98 (260.4)	<.0001
Total visits	1.60 (1.72)	245.0 (265.4)	2.19 (2.03)	328.4 (302.0)	<.0001
Diagnostic tests, mean (SD)					
Sinus x-ray	0.73 (0.86)	16.8 (19.7)	0.99 (0.88)	22.7 (20.2)	<.0001
Sinus CT	0.13 (0.34)	15.9 (43.6)	0.23 (0.46)	29.8(58.9)	<.0001
Microbiological culture	0.04 (0.21)	0.9 (4.9)	0.10 (0.35)	2.3 (8.0)	.0004
Anterior rhinomanometry	0.01 (0.10)	0.9 (9.0)	0.01 (0.13)	1.2 (11.9)	.6918
Acoustic rhinometry	0.01 (0.10)	0.1 (1.6)	0.00 (0.05)	0.04 (0.8)	.3575
Peak nasal inspiratory flow	0.00 (0.06)	0.06 (1.0)	0.00 (0.03)	0.02 (0.6)	.2788
Olfactometry (BAST-24)	0.01 (0.10)	1.4 (22.8)	0.01 (0.11)	2.1 (24.4)	.5829
Skin prick test	0.06 (0.30)	2.0 (10.5)	0.11 (0.34)	3.8 (11.9)	.0042
Total diagnostic tests	0.98 (1.15)	38.1 (64.4)	1.46 (1.32)	61.9 (78.8)	<.0001
Drug therapy, mean (SD)					
Antibiotics	0.79 (0.71)	12.9 (11.6)	0.98 (0.69)	16.0 (11.2)	<.0001
Intranasal corticosteroids	0.41 (0.56)	6.1 (8.2)	0.65 (0.66)	9.4 (9.7)	<.0001
Oral H ₁ antihistamines	0.35 (0.55)	3.3 (5.2)	0.55 (0.66)	5.2 (6.2)	<.0001
Nasal decongestants	0.43 (0.59)	2.0 (2.7)	0.57 (0.65)	2.6 (2.9)	.0002
Mucolytic	0.55 (0.63)	2.4 (2.7)	0.72 (0.67)	3.1 (2.9)	<.0001
Saline solution	0.46 (0.61)	1.0 (1.3)	0.66 (0.68)	1.5 (1.5)	<.0001
Phytotherapy	0.45 (0.56)	11.6 (14.4)	0.50 (0.58)	13.0 (15.1)	.0941
Total drug therapy	3.45 (2.13)	39.2 (25.9)	4.63 (2.22)	50.8 (25.3)	<.0001
Total cost, mean (SD)	-	322.3 (301.2)	-	441.1 (344.3)	<.0001

Abbreviations: ARS, acute rhinosinusitis; BAST-24, Barcelona Smell Test – 24 Odors

^aArithmetic mean (SD) of medical visits, diagnostic tests, and drug packages per patient

^bArithmetic mean (SD) of cost per episode and patient.

^ct test comparing mean costs between viral and postviral ARS.

(62% vs 76%), nasal corticosteroids (38% vs 54%), antihistamines (31% vs 46%), nasal decongestants (38% vs 48%), mucolytics (48% vs 60%), nasal saline (40% vs 54%), and nasal phytotherapy (41% vs 46%) (summarized from reference 21). The costs related to the medications prescribed were higher in postviral ARS (€50.83 [25.30], $P<.001$) than in viral ARS (€39.2 [25.9]) (Table 3). The differences in direct costs related to the medications prescribed were also statistically significant between the severity groups. For viral ARS, the costs were €31.3 (21.6) for mild episodes, €36.1 (24.1) for moderate episodes, and €43.8 (27.8) for severe episodes ($P=.0023$). For postviral ARS, the costs were €33.5 (12.7) for mild episodes, €49.4 (25.8) for moderate episodes, and €52.5 (24.8) for severe episodes ($P<.0239$) (Figure 2, in red). Regarding over-the-counter medications, close to half a pack of medication was observed in both groups, at a cost of around €3, with no statistically significant differences. The most frequent over-the-counter products were nasal decongestants and nasal saline. For all the groups and for all the medications, the cost of over-the-counter medications was significantly lower than that of prescribed medications (data not shown). When we compared correct and incorrect treatment, a higher cost for incorrect treatment was observed (Table 4).

Extrapolated direct costs of ARS in Spain per year: As explained in Material and Methods, we extrapolated the annual direct cost of ARS in Spain considering the percentages of ARS patients consulting their doctor. According to this estimate, the annual direct costs of postviral ARS in Spain would be ~€300 or ~€600 million, while the annual direct cost of common cold would be ~€2900, ~€7200, or ~€9700 million, depending on the percentage of patients consulting with their doctors (Table 5).

Discussion

The main findings of the PROSINUS cost analysis can be summarized as follows: (1) the overall direct costs of postviral ARS (~€440) were higher than those of viral ARS (~€320); (2) the direct costs of severe viral ARS (~€380) were higher than those of moderate (~€275) and mild (~€220) viral ARS; (3) the direct costs of severe postviral ARS (~€500) were higher than those of moderate (~€380) and mild (~€310) postviral ARS; and (4) two thirds of the overall direct costs of ARS resulted from medical visits (~€245 in viral ARS and ~€330 in postviral ARS), followed by the use of diagnostic tools (~€40 and ~€60), and medications prescribed (~€40 and ~€50), respectively.

Table 4. Comparison Between the Cost of Correct and Incorrect Medication for Treating Viral and Postviral Nonbacterial Uncomplicated ARS

	Correct medication (n=120) Cost (€) ^a	Incorrect medication (n=1231) Cost (€) ^a	<i>P</i> value ^b
Viral ARS (n=494)			
Antibiotics	0.00 (0.00)	13.92 (11.43)	<.0001
Nasal corticosteroids	0.00 (0.00)	6.52 (8.28)	.0001
Antihistamines	4.33 (6.23)	3.22 (5.11)	.2228
Nasal decongestants	3.00 (2.91)	1.90 (2.64)	.0188
Mucolytics	1.60 (2.36)	2.43 (2.74)	.0813
Nasal saline	1.63 (1.45)	0.96 (1.32)	.0042
Phytotherapy	23.03 (16.41)	10.71 (13.91)	<.0001
Total drug therapy	33.59 (13.61)	39.66 (26.56)	.1821
Postviral ARS (n=857)			
Antibiotics	0.00 (0.00)	17.80 (10.38)	<.0001
Nasal corticosteroids	9.96 (9.87)	9.35 (9.65)	.5872
Antihistamines	6.36 (6.61)	5.12 (6.16)	.0817
Nasal decongestants	2.84 (2.90)	2.55 (2.95)	.3863
Mucolytics	2.54 (2.60)	3.18 (2.90)	.0491
Nasal saline	1.68 (1.58)	1.42 (1.49)	.1334
Phytotherapy	17.44 (17.20)	12.49 (14.77)	.0041
Total drug therapy	40.81 (17.04)	51.93 (25.82)	.0001

Abbreviation: ARS, acute rhinosinusitis.

^aArithmetic mean (SD) per patient.

^bt test comparing mean costs.

Table 5. Estimated Direct Costs of Viral and Postviral ARS per Year in Spain by Percentage of Patients Who Consult Their Doctor^a

	10%	25%	33.3%
Viral ARS			
Medical visits	2205	5513	7350
Diagnostic tools	343	857	1143
Treatment	353	882	1176
TOTAL	2901	7252	9669
Postviral ARS			
Medical visits	230	460	
Diagnostic tools	43	87	
Treatment	36	71	
TOTAL	309	618	

Abbreviation: ARS, acute rhinosinusitis.

^aAll values expressed in millions of euros.

Other authors have also found the main part of direct costs of ARS to be attributable to medical visits [16].

In the present study, we only analyzed patients with ARS episodes who were consulting a physician, while in real life, an unknown proportion of patients affected by viral or postviral ARS never consult a doctor. The patients consulting a doctor probably have more severe symptoms, thus entailing a risk of bias when extrapolating the costs of ARS to the general population. In a recent study in children in the Netherlands aged up to 4 years, Peetoom et al [24] described how ~70%

of those with infectious symptoms such as runny nose, stuffed nose, sneezing, or cough never consult a doctor. Despite the risk of bias, analysis of the proportions of patients consulting doctors enables us to extrapolate a total cost of postviral ARS of between €300 and €600 million and between €2900 and €9700 million for common cold, ie, considerably high (Table 5). These values account for 3% of the 2019 gross domestic product of Spain (€1 244 757 million); therefore, the real cost is probably overestimated, with values being in the upper range. In any case, they do suggest that ARS entails a high economic burden.

Although it has been demonstrated that rhinosinusitis is one of the main diseases responsible for work absenteeism, comparable with chronic bronchitis or allergic rhinitis [16], very few studies have examined the economic burden of ARS. In 1990, the costs attributable to ARS in the US reached US\$3390 million per year [19]. In Europe, a recent study from Sweden reported a total cost of ~€1100 per ARS episode, 75% (~€1000) of this being attributable to indirect costs and 25% (~€265) to direct costs [20]. Although the PROSINUS study did not analyze indirect costs, the estimation based on Stjärne et al [20] revealed that the total cost per episode, including both direct (25%) and estimated indirect (75%) costs, would be ~€1200 per viral episode (common cold) and ~€1700 per postviral ARS episode.

Other studies have analyzed the costs of other nasal inflammatory diseases such as allergic rhinitis and CRS. Colás et al [25] found that the cost attributable to allergic rhinitis in Spain was €2327 per patient and year, being higher for persistent allergic rhinitis (€2656) than for intermittent allergic rhinitis (€1485) and for indirect costs (€1773) than direct costs (€554). In the US, without considering the cost related to endoscopic sinus surgery, direct costs per patient and year for CRS were US\$800 compared with US\$2-3000 for indirect costs [26].

Some studies have also analyzed the costs of other acute inflammatory ENT diseases such as acute otitis media and acute tonsillitis. In 2014, Tong et al [27] reported the direct cost of an acute otitis media episode as being US\$218, while Duarte et al [28] reported a total cost of US\$1685 per patient and year with acute tonsillitis in the pediatric population, including the cost of parental absenteeism. While ARS is an uncomplicated and self-limiting disease, our data confirm that its cost impact is similar to that of other acute inflammatory ENT diseases.

These findings suggest a clear unmet need to reduce the costs of ARS management. Given the need for a decrease in the number of medical visits, health education should be improved in the general population by spreading the message that ARS is a self-limiting and uncomplicated disease requiring only symptomatic treatment in most cases. Visits to the doctor should be limited to severe episodes (ie, high fever, severe facial pain) and complicated episodes (ie, ocular, neurological). On the other hand, the costs associated with diagnostic tests and prescription of medications are directly linked to medical management, with family physicians and ENT specialists the main educational target for decreasing these costs. In their randomized trial from 2012, Svensson et al [17] compared the cost of treating ARS with intranasal corticosteroids and amoxicillin and showed that the cost of the corticosteroid group was much lower. Cramer et al [18] analyzed the annual

cost associated with antibiotic use for ARS between 2006 and 2010, reporting a burden of US\$352 million per year, which decreased dramatically to US\$166 million when clinicians followed guideline recommendations. In this study, we found incorrect treatment to be related to higher costs than correct treatment, the difference being around €6 per patient in viral ARS and around €11 per patient in postviral ARS (Table 4). Therefore, guideline recommendations for appropriate management of ARS should be disseminated in order to avoid overuse of diagnostic tools other than rhinoscopy and nasal endoscopy (ie, imaging, microbiology). By using these measures, ~€40 to ~€80 million could be saved annually for postviral ARS and ~€300 to €1100 million could be saved for the common cold. Regarding prescription of medications, by simply avoiding the use of mucolytics and antihistamines, which are not recommended for treatment of ARS, the savings would be from ~€5 to ~€10 million for postviral ARS and from ~€50 to ~€170 million for viral ARS (common cold). Furthermore, avoidance of nonindicated antibiotics might induce significant savings in nonbacterial ARS, ranging from ~€10 to ~€20 million for postviral ARS and from ~€100 to ~€350 million for viral ARS (common cold).

As in most epidemiological studies, our findings are subject to a series of limitations. First, only direct costs were analyzed. However, although costs can vary considerably between countries and cannot therefore be fully extrapolated, if it is considered that direct costs represent only 25% of the overall cost, as stated elsewhere [20], the annual cost in Spain for postviral ARS would range from ~€1200 to ~€2400 million for postviral ARS and from ~€11 600 to €38 600 million for viral ARS (common cold). Second, the study population cannot be considered a random sample, since there was no control over which patients received specific medications or in which patients the diagnostic tests were performed. Third, only medical direct costs were evaluated, while other direct nonmedical costs were not. Moreover, it must be considered that the frequency distribution of severity cannot be applied to the general population, since patients consulting their doctors may have more severe disease than those who decided not to consult. Fourth, the fact that a high number of patients were rejected from the initial screening or lost after Visit 1 may lead to a bias. Our study also has a series of strengths, namely, the high number of patients included, the use of the EPOS definitions of diagnosis as inclusion criteria, the classification into both viral and postviral populations, and the fact that we performed a real-life and prospective study providing physicians with real-world data on management of the disease in daily clinical practice.

In conclusion, while uncomplicated and self-limiting, ARS is associated with a considerable socioeconomic burden for the Spanish Health System. This burden could be decreased with the dissemination of guideline recommendations and implementation of educational programs among patients and physicians (both family physicians and ENT specialists).

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Conflicts of Interest

JM is or has been a member of advisory boards, received speaker fees and clinical trial funding or research grants from Allakos, AstraZeneca, Genentech, GlaxoSmithKline, Menarini, Mitsubishi-Tanabe, MSD, Mylan-MEDA Pharma, Novartis, Sanofi-Genzyme, Regeneron, UCB, and the Uriach Group. The remaining authors declare that they have no conflicts of interest.

Previous Publications

A partial pharmacoeconomic study on the use of phytotherapy in ARS has been published with data from the PROSINUS study [Mullol J, Crespo C, Carré C, Brosa M. Pharmacoeconomics of *Cyclamen europaeum* in the management of acute rhinosinusitis. *Laryngoscope* 2013;123(11):2620-5]. Another article with data from the PROSINUS study highlights the overuse of diagnostic tools and treatment in viral and postviral ARS, compares management between primary care physicians and ENTs, and compares this management with the main international guidelines [Jaume F, Quintó L, Alobid I, Mullol J. Overuse of diagnostic tools and medications in acute rhinosinusitis in Spain: a population-based study (the PROSINUS study). *BMJ Open*. 2018;8(1):e018788]. The direct cost data reported in this manuscript have not been previously published in any medical journal. However, partial reports were presented at scientific meetings as oral presentations and poster discussions, as follows:

- 26th Congress of the European Rhinologic Society (ERS), 35th International Symposium of Infection and Allergy of the Nose (ISIAN), and 17th Congress of the International Rhinologic Society (IRS). Stockholm (Switzerland), July 3-7th, 2016.
- Jaume F, LI Quintó, C Langdon, M López, I Alobid, J Mullol. Abuse of diagnostic tools and therapeutic medications in mild and moderate acute rhinosinusitis in Spain. The PROSINUS study. (Poster Discussion)
- Jaume F, LI Quintó, C Langdon, M López, I Alobid, J Mullol. Association of different medications used in real-life clinical practice with duration, quality of life, and complications of acute rhinosinusitis. The PROSINUS study. (Poster Discussion)
- XI Congreso de la Sociedad Hispano-Alemana de Otorrinolaringología y Cirugía Cervico-Facial. Dusseldorf, 2-3 May 2016
- Jaume F, Quintó L, Mullol J. Abuso diagnóstico y terapéutico en el manejo de la Rinosinusitis aguda en España. Estudio PROSINUS. (Oral Presentation)

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