BMJ Open

Abuse of diagnostic tools and medications in acute rhinosinusitis: a population based study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018788
Article Type:	Research
Date Submitted by the Author:	07-Aug-2017
Complete List of Authors:	Jaume Monroig, Francesca; Hospital Clinic, Universitat de Barcelona, Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Immunoal.lèrgia Respiratòria Clínica i Experimental Quintó, Llorenç; Institut de Salut Global de Barcelona (ISGlobal) de Recerca en Salut Internacional de Barcelona (CRESIB); Centro de Investigación Biomédica En Red en Epidemiología y Salud Pública (CIBERESP). Alobid, Isam; Hospital Clinic, Universitat de Barcelona, Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Immunoal.lèrgia Respiratòria Clínica i Experimental Mullol i Miret, Joaquim; Hospital Clínic, Universitat de Barcelona, Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Immunoal.lèrgia Respiratòria Clínica i Experimental
Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Infectious diseases, Medical management
Keywords:	acute rhinosinusitis, common cold, antibiotics, intranasal corticosteroids, phytotherapy, PROSINUS

Abuse of diagnostic tools and medications in acute rhinosinusitis: a population based study

Francesca Jaume Monroig, research fellow,[1,2] **Llorenç Quintó**, statistician,[4,5] **Isam Alobid**, professor of otorhinolaryngology,[1,2,3] **Joaquim Mullol i Miret**, professor of research.[1,2,3]

1) Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia, Hospital Clínic, Universitat de Barcelona, Barcelona, Catalonia, Spain; 2) Immunoal.lèrgia Respiratòria Clínica i Experimental, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain; 3) Centro de Investigación Biomédica En Red en Enfermedades Respiratorias (CIBERES); 4) Institut de Salut Global de Barcelona (ISGlobal) de Recerca en Salut Internacional de Barcelona (CRESIB), Barcelona, Catalonia, Spain; 5) Centro de Investigación Biomédica En Red en Epidemiología y Salud Pública (CIBERESP).

CORRESPONDING AUTHOR:
Joaquim Mullol i Miret, MD, PhD. Unitat Rinologia i Clínica de l'Olfacte, ENT Department, Hospital Clínic, IDIBAPS, Villarroel 170, 08036 Barcelona, Catalonia, Spain. Tel: +34 932 279 872, Fax: +34 932 279 813, e-mail: jmullol@clinic.cat

ABSTRACT

Objectives. Acute rhinosinusitis (ARS) has a high incidence. Diagnosis is clinical, and evolution mostly self-limited. The aim of this study was to describe socio-demographic characteristics, and use of diagnostic tools and medications in patients with ARS.

Design. Prospective observational study in real life clinical practice.

Setting. Patients with clinical diagnosis of ARS (N=2,610) were included from ENT clinics in Spain. A second visit at resolution was done.

Participants. Patients were classified according to the duration of symptoms: viral ARS (≤10days), postviral ARS (>10days, ≤12weeks), chronic RS (>12weeks).

Main outcome measures. Socio-demographic characteristics, symptoms, disease severity, quality of life (SNOT-16), used diagnostic tools and medications were assessed. The management performed by Primary Care Physicians (PCPs) and by Otorhinolaryngologists (ORLs) were compared.

Results. Patients were classified as viral (36%) and postviral (63%) ARS, and 1% as chronic. Working in a poorly air-conditioned environment was a risk factor [Odds Ratio (OR)=2.26] in developing postviral ARS. A higher number of diagnostic tools (rhinoscopy/endoscopy 80%vs.70%; plain X-ray 70%vs.55%; CT scan 22%vs.12%; p-values<0.0001) were performed in postviral than viral cases. PCPs performed more X-rays than ORLs (p<0.0001). ARS patients, more those with postviral than viral disease, received a high number of medications (oral antibiotics: 76%vs.62%; intranasal corticosteroids: 54%vs.38%; antihistamines: 46%vs.31%; mucolytic 48%vs.60% (p-

values<0.0001). PCPs prescribed more antibiotics, antihistamines, and mucolytics than ORLs (p-values<0.0068). More patients with postviral than viral ARS reported symptoms of potential complications (1.5%vs.0.4%, p=0.0603). Independently of prescribed medications QoL was more affected in postviral (38.7±14.2 vs. 36.0±15.3, p=0.0031) than viral ARS and ARS resolution was obtained after 6.04 (viral) and 16.55 (postviral), days with intranasal corticosteroids being associated with longer (OR=1.07) and phytotheraphy with shorter (OR=0.95) duration.

Conclusions. This study suggests a significant abuse of therapeutic tools and prescribed medications, predominantly oral antibiotics, by PCPs and ORLs, and for viral and postviral ARS.

STRENGHTS AND LIMITATIONS:

- Strengths:
  - Real life prospective study
  - High number of patients included
  - Classifying the patients following EPOS criteria
- Limitations:
  - The groups are not random samples
  - The management of PCPs and ORLs can not directly be compared as they treat the same patients but in different time of disease.

KEYWORDS: acute rhinosinusitis, common cold, antibiotics, intranasal corticosteroids, phytotherapy, PROSINUS.

INTRODUCTION

Rhinosinusitis is an inflammatory process of the paranasal sinuses with high prevalence in clinical practice[1] and a significant impact on quality of life.[2,3] Acute rhinosinusitis (ARS) is mainly an inflammatory disease, usually caused by a viral infection, although other processes such allergic rhinitis, anatomical abnormalities, nasal polyps, tobacco smoke, or nasal decongestant abuse can constitute predisposing factors.[1] Viral ARS (common cold) is usually self-resolved and accounts for most of ARS cases.[4] Postviral ARS occurs as a perpetuation of the inflammatory condition, even when the viral agent has gone.[5] Only a small percentage of the latter (0.5-2%) actually lead to acute bacterial rhinosinusitis (ABRS).[6,7] The incidence of ARS is very high, adults having between two to five common cold episodes per year[8], while the incidence of postviral ARS has been reported to be 3.4 cases per 100 inhabitants/year.[9] Orbital, osseous, or intracranial complications may occur, but their incidence is very low (about 3 cases per million people).[10]

The diagnosis of ARS is based on the clinical history of a sudden onset of nasal symptoms (nasal congestion/obstruction/blockage, rhinorrea/postnasal drip, facial pain/pressure, and/or reduction/loss of smell) supported by physical examination.[1] Microbiological or imaging studies are not required,[11,12], with imaging being indicated when symptoms suggesting complications appear.[1]

The goals of ARS treatment are to provide symptomatic relief, accelerate time of remission, and prevent complications. Although antibiotics have traditionally been the treatment most often indicated for ARS, there is no evidence that antibiotics are significantly better than placebo in viral (common cold) and

postviral ARS[13]. In fact, a number of bacterial ARS cases have been resolved without antibiotics at all.[14,15] Furthermore, the use of antibiotics does not prevent complications.[10] Indeed, their overuse can lead to a number of side effects and to an increase of antibiotic resistance.[16] In the last two decades several studies have demonstrated that the addition of intranasal corticosteroids to antibiotics, or even intranasal corticosteroids in monotherapy, may provide an excellent option to treat postviral ARS.[17;18] Accordingly, European position paper on rhinosinusitis and nasal polyps (EPOS) 2012 recommended symptomatic relievers (analgesics, saline serum, and decongestants) for viral/common cold cases, intranasal corticosteroids for postviral cases, and the addition of oral antibiotic for bacterial/complicated cases or well-established complications.[19,20] Recent studies have shown that selected herbal medicines (phytotherapy) may constitute an additional medical option to treat viral/postviral ARS.[21-24] However, a number of very commonly used medications such as mucolytics, antihistamines, probiotics, or vitamin C have not shown any evidence of efficacy in ARS.[1]

The objectives of the PROSINUS study were: 1st) to describe and compare the diagnostic tools and therapeutic medications used by primary care physicians (PCPs) and Otorhinolaryngologists (ORLs) to manage viral or postviral ARS in Spain, 2nd) to assess the risk factors leading to postviral ARS, and 3rd) to assess the evidence of the efficacy of those medications most often used to decrease disease duration and prevent complications in patients with viral or postviral ARS.

METHODOLOGY

Study design, participants, and setting.

The *"PROspective epidemiological study about the diagnosis and therapeutic management of Acute RhinoSINUsitis in otorhinolaryngology clinics in Spain (PROSINUS study)"* is a prospective, real life, and descriptive study that analysed a cohort of patients (N=2,610) with acute ARS in Spain. Patients were classified as suffering from viral (common cold) or postviral ARS. Otorhinolaryngologists (N=284) from throughout Spain participated in the study. Each ORL represented 9.2±1.8 patients (range 1-11).

To define and classify rhinosinusitis we used the definitions provided by EPOS *(European Position Paper on Rhinosinusitis and Nasal Polyps)* consensus.[25] ARS was clinically defined by a sudden onset of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or anterior/posterior nasal discharge. Additional symptoms could be facial pain/pressure and/or reduction/loss of smell. Three different phenotypes of ARS were defined. Viral ARS (common cold) was defined as the presence of symptoms of rhinosinusitis for less than 10 days, postviral ARS was as symptoms lasting for >10 days and <12 weeks, and chronicity when symptoms lasted for ≥12 weeks. Disease severity was assessed by using a visual analogue scale (VAS, 0-10cm) and classified as mild (VAS 0-3cm), moderate (VAS >3-7cm), or severe (VAS >7-10cm).[1, 26]

Inclusion criteria. Patients of both gender, ≥18 years old, who come to see the ORL with symptoms consistent with the clinical diagnosis of viral/postviral ARS according to the EPOS criteria.[25]

Exclusion criteria. Patients with exacerbations of diagnosed CRS, with clinical suspicion of bacterial ARS (severe cases with fever >38ºC or unilateral severe pain), or patients not able to do follow-up visits or with a high risk of dropout.

Study visits. Patients were included between January 2007 and March 2008. Visit 1 was done at inclusion, while visit 2 was done after 2-4 weeks of inclusion. Where patients still had symptoms at visit 2, a visit 3 was performed after 12 weeks of inclusion.

Patient's involvement. Participants were involved in the study on the basis of daily clinical practice. Patients did not participate in the design of the study.

Ethics. The Ethics Committee of our institution *(Comité Ètic de Investigació Clínica de l'Hospital Clínic de Barcelona: CEIC)* approved the study (2006/3305) and all patients signed the informed consent.

Measurements, and Outcomes

At Visit 1, socio-demographic and anthropometric characteristics, duration of symptoms (days), severity of disease, quality of life (SNOT-16), diagnostic tools used, and medications prescribed before inclusion by PCPs were recorded. The

general health status prior to and during the disease was also recorded. At Visit 2, the duration of episode (number of days), symptoms addressing potential complications, diagnostic tools used and medications prescribed between visits 1 and 2 by ORLs, severity of disease, and quality of life (SNOT-16) were also recorded. Where Visit 3 was required (based on no resolution at Visit 2), the time of disease resolution or chronification was recorded.

Demographic Characteristics. At Visit 1 the following characteristics were recorded: age (years), gender, area of residence (rural, <2,000 inhabitants; semi-rural, 2,000-10,000 inhabitants; and urban, >10,000 inhabitants), education level (no education or unfinished, primary or secondary education, and higher education or college), workplace environment (proper air-conditioning, poorly air-conditioning, outdoor work, unemployed), social and family circumstances (living as part of a family or in a partnership, single, living in an institution or residence, or living in shared housing), home environment (well-heated, airy).

Use of diagnostic tools. We recorded the use of anterior rhinoscopy or nasal endoscopy (to assess oedema, congestion, or mucopurulent secretion from the middle meatus), imaging techniques (X-ray, CT scan), and microbiological cultures (culture of nasal secretions). This information was recorded at Visits 1 and 2 in order to know the tests performed before (by PCPs) and after (by ORLs) the inclusion in the study.

Prescription of medications. Prescribed medications, either recommended (antibiotics, intranasal corticosteroids, nasal saline irrigation, nasal decongestants, phytotherapy) or non-recommended (antibiotics, antihistamines, mucolytics) by EPOS consensus to treat ARS, were recorded at Visits 1 and 2.

Episode duration and disease severity. Duration of symptoms (days) was recorded at Visits 1 and 2, as at Visit 3 when needed. Severity was assessed at Visits 1 and 2 by using a visual analogue scale (VAS, 0-10cm)[1] after answering the question *"how troublesome are your symptoms of rhinosinusitis?"* (0, not troublesome, to 10, worst imaginable).

Quality of Life and health status. Sino-nasal Outcome Test (SNOT)-16 questionnaire was used to assess the impact of disease and its treatment on quality of life at both Visits 1 and 2. Each of the 16 items was scored from 0 (not affected) to 5 (extremely affected). The overall score runs from 0 (better QoL) to 80 (worst QoL). The general health status prior to and during the disease was recorded using a visual analogical scale (0-10cm).

Disease complications. Instead of recording the presence of complications, the study recorded the presence of symptoms linked to complications, as stated by EPOS guidelines.[25] Orbital symptoms (palpebral oedema, orbital pain, diplopia, exophthalmos, decrease in visual acuity), neurological symptoms (meningeal symptoms, neurological deficit), and frontal symptoms (frontal oedema, severe frontal pain) were assessed. In addition, other sinonasal signs and symptoms of a potential different disease involved were also recorded

(unilateral symptoms, bleeding, crusts, lacrimation and conjunctiva hyperemia, or cacosmia).

Data management & statistical analysis

Study size. This was an observational study, initially posed as a pilot study without a specific hypothesis as the main objective. Therefore, the sample size was determined by logistical and cost reasons rather than by analytical criteria.

Sociodemographic characteristics, nasal symptoms, use of diagnostic tools, prescribed medications, disease severity, and quality of life were compared between patients with viral (common cold) and postviral RSA. Differences in quantitative measures were evaluated by Student's t test for independent groups and differences in qualitative measures were assessed with the Chi-square or Fisher's exact test as appropriate. The improvement in patient's quality of life (SNOT-16) between Visits 1 and 2 was evaluated by Student's t test for paired groups.

Logistic regression models were estimated to assess the associations with postviral RSA using viral RSA as the reference group. The relationship between treatments (medication) and disease duration, quality of life at Visit 2 and the risk of complications were also assessed. These associations were evaluated by linear regression using the duration and the total score of SNOT-16 in logarithmic scale, and by logistic regression for the complications assessment. Multivariate regression models were estimated by a backward selection

procedure using 0.05 as significance level for removal from the model. All regression models were adjusted for the study group (viral and postviral ARS). Additionally, regression models to evaluate associations between medication and duration, or medication and complications, were also adjusted for severity at recruitment, whereas models to evaluate associations between medication and quality of life at Visit 2 were adjusted for quality of life at visit 1. Interactions between treatments were also assessed. Statistical analysis was performed using Stata version 14 (Stata Corp., Texas, USA).

RESULTS

Demographic characteristics

From the initial 1,678 patients included at Visit 1, 1,499 (89%) completed Visit 2, with 1,362 patients being considered valid for the study **(Figure 1**). Patients were classified into three groups according to the duration of symptoms of rhinosinusitis: 36% (n=494) had viral ARS (common cold) with a mean duration of 6.0 days (95%CI: 5.9-6.2), 63% (n=857) had postviral ARS with a mean duration of 16.5 days (95%CI: 15.8-17.3), and 1% (n=11) had chronic symptoms (CRS). Patients with CRS were excluded from this analysis and therefore the sample size for analysis was 1,351 patients (36% with viral and 63% with postviral ARS). By definition, all patients with viral ARS were cured before 10 days. From those with postviral ARS, 74.3% of episodes were resolved before Visit 2, and 25.7% in the time between Visits 2 and 3 **(Figure 1**).

More women (53%) than men participated in the study, with a similar ratio appling to both viral and postviral ARS sample groups. Both groups were also homogenous concerning weight, height, or ethnicity. Most patients (81%) lived in an urban environment, with no differences between disease groups (**Table 1**). Concerning workplace, most patients with either viral (68%) or postviral (63%) ARS worked in a well air-conditioned environment. Patients working in a poorly air-conditioned environment were significantly higher in postviral (13%) than viral (8%) ARS, p=0.0092. Half of patients (46%) reported a previous history of ARS episodes without differences between groups.

Nasal symptoms

Nasal congestion/obstruction/blockage (98%) and anterior/posterior nasal discharge (95%) were the most frequent symptoms of ARS, followed by facial pressure/pain (77%) and reduction/loss of smell (60%). No differences were found between patients with viral and postviral ARS (**Table 2**). By excluding nasal discharge in the postviral ARS group, the frequency of symptoms were however significantly higher ($p<0.05$) when disease severity increased, and this was more relevant for hyposmia and facial pressure/pain in postviral ARS **(Figure 2).**

Disease severity

Severity by VAS for postviral ARS was slightly higher (7.13±1.48cm) than for viral ARS (6.98±1.60cm), although this was not statistically significant**.** The general health status (VAS) during the disease episode was also similar in viral (5.45±1.89cm) and in postviral ARS (5.59±1.89cm), but significantly affected when compared to the general health status they had retrospectively, before the episode (8.85±1.40cm and 8.67±1.76cm, respectively).

When comparing viral and postviral ARS, all three levels of severity were similar (mild: 2.65±0.57cm vs 2.72±0.57cm; moderate: 6.11±0.97cm vs 6.09±1.00cm; and severe: 8.36±0.60 vs 8.35±0.64). In addition, no differences were found between viral and postviral ARS in general health status (VAS) in the three severity levels, either before (retrospective) or during the disease.

Quality of life (SNOT-16)

At Visit 1, SNOT-16 global score was worse in postviral (38.7±14.2, p=0.0031) than in viral RSA (36.0±15.3). In addition, a higher SNOT-16 score was strongly related to a higher disease severity degree in both viral and postviral ARS (p<0.0001)**.** At Visit 2, SNOT-16 global score significantly improved compared to Visit 1 for both postviral (15.9±15.9, p<0.0001) and viral ARS (14.1±17.2, p<0.0001). No significant differences (p=0.0726) between viral and postviral groups were found for the SNOT-16 score (**Figure 5).**

Diagnostic tools

Overall, including all tests conducted before and after patients were recruited for the study, the diagnostic tools most frequently performed were anterior rhinoscopy/nasal endoscopy (76%), X-ray (64%), CT scan (18%), and microbiology cultures (7%)**,** with all of them being more frequent (p<0.0002) in postviral than in viral ARS (**Figure 3**). PCPs performed more X-ray (45% vs. 36%, p<0.0001) than ORLs, who performed more rhinoscopy/endoscopy (68% vs. 27%, p<0.0001), CT scans (15% vs. 5%, p<0.0001), and microbiology cultures (5% vs. 2%, p<0.0001). Concerning disease severity, the performance of X-ray increased with higher levels of severity in postviral (p=0.0045) but not in viral (p=0.0606) ARS. In contrast, the performance of CT-scan increased with higher severity levels in viral (p=0.0024) but not in postviral ARS (p=0.2631).

Medications

In viral and postviral ARS, the most frequently prescribed medication was, respectively, oral antibiotic (62% vs. 76%), topical steroids (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%). All drugs were more frequently prescribed in postviral than in viral ARS patients ($p<0.0006$ for all comparisons), except for nasal phytotherapy ($p= 0.1413$) **(Figure 4).**

There were only a few patients (3%) who did not receive any treatment, while most of ARS patients received more than one medication. Based on EPOS recommendations, oral antibiotics were incorrectly prescribed in 62% of viral ARS (common cold), while only 54% of postviral ARS patients were treated with intranasal corticosteroids **(Table 3).**

In addition, PCPs prescribed more oral antibiotics (53% vs. 39%, $p<0.0001$), antihistamines (26% vs. 22%, $p=0.0068$), nasal decongestants (34% vs. 18%, $p<0.0001$), mucolytics (45% vs 21%, $p<0.0001$), and intranasal saline (34% vs. 25%, $p<0.0001$) than ORLs. However, ORLs prescribed more nasal phytotherapy (39% vs. 9%, $p<0.0001$) and showed a tendency to prescribe more intranasal corticosteroids (30% vs. 26%, $p=0.0721$) than PCPs **(Figure 4).**

Concerning disease severity, antibiotics and mucolytics were more frequently prescribed in severe cases of both viral and postviral ARS ($p<0.0225$ for all comparisons), while antihistamines were more prescribed in severe viral ARS ($p=0.0040$), and nasal decongestants ($p=0.0408$) in severe postviral ARS.

No significant association was found between medication and quality of life

(SNOT-16 score) or the risk of complications at visit 2. Interactions between treatments were also assessed, although none of them showed a statistically significant difference.

Disease complications

More patients with postviral (1.5%) than viral ARS (0.4%) had signs or reported symptoms potentially linked to rhinosinusitis complications, such us ophthalmic, neurological, or frontal (p=0.0603). In addition, there were patients who reported other unusual signs and symptoms (5.6% in postviral and 3% in viral ARS) that could potentially be linked to a different diagnosis **(Table 4).** No differences were found when comparing disease severity degrees.

Factors associated with disease duration

All population characteristics were analysed to identify factors associated with postviral ARS development. **Table 5** shows the crude estimates for Odds Ratios using viral ARS as a reference group. In the multivariate analysis we found that working in a poorly air-conditioned enclosure was the only factor significantly associated with developing postviral ARS (OR: 2.26; 95%CI: 1.27-4.04).

The analysis of associations between medication and duration, adjusted for type of RSA (viral / postviral) and severity at baseline, showed a longer duration of the episode in patients who took nasal decongestants, saline solutions, antibiotics or intranasal corticosteroids than in those who did not. According to multivariate analysis, phytotherapy (mainly *Cyclamen europaeum, CE*) was related with shorter duration (Odds Ratio: 0.95 [0.91-1.00], p=0.0480), although

intranasal corticosteroids were related with longer duration (Odds Ratio: 1.07 [1.02-1.12], p=0.0048).

DISCUSSION

The most significant findings of the PROSINUS study were: 1st) ARS was mostly a self-limited disease, with only 1% of chronification; 2nd) working in a poorly air-conditioned environment was a risk factor for common cold to develop into postviral ARS; 3rd) both PCPs and ORLs performed a high number of non-indicated diagnostic tools, mainly plane X-Ray; 4th) ORLs and especially PCPs prescribed a large number of non-recommended medications, with antibiotics being the most significant, followed by mucolytics and antihistamines; 5th) intranasal corticosteroids were less frequently prescribed by ORLs and even less so by PCPs; and 6th) there was an association between prescribed intranasal corticosteroids and a longer duration of ARS, and prescribed phytotherapy (*CE)* and shorter disease episodes.

In the present study only 1% of chronification was found, suggesting that most ARS cases tend to be cured independently of the prescribed treatment. Spontaneous cure with no treatment has been identified in 80% of ARS patients[27]. Working in a poorly air-conditioned environment was the only identified risk factor (OR: 2.26) in developing postviral ARS. Previous studies have suggested the importance of other factors such as contact with people with upper respiratory complaints[28], winter months (January to March) having a risk factor (OR: 2.9) to develop ARS compared to July to September[29], allergic rhinitis developing in postviral ARS (OR: 4.4) compared to healthy controls[30], and active[31] and passive[32] smoking. In our study the most prevalent symptoms, in both common cold and postviral ARS, were nasal congestion

(98%) and discharge (95%), followed by facial pressure/pain (77%) and smell loss (60%). Although the presence of nasal symptoms was biased by inclusion criteria, facial pressure/pain and smell loss were highly associated with severe ARS. In a French study done by PCPs, similar findings were reported in patients with Acute Maxillary Sinusitis.[2] Despite the EPOS guidelines[1] stating that the diagnosis of ARS is mainly clinical (based on symptoms) and supported by nasal examination (anterior rhinoscopy or nasal endoscopy), in our study, many ORLs and particularly PCPs did not perform nasal examination (68% and 27% respectively) in ARS patients. Plain X-ray has proven to have poor sensitivity and specificity[33,34] and is not recommended in the diagnosis of ARS[35]. Since Gwaltney et al.[36] reported that CT scans show sinus opacity in most patients (87%) with common cold, this imaging technique is only recommended in complicated cases [11]. The present study shows however that physicians from Spain performed a high number of plain X-ray and CT scan in postviral ARS (70% and 22%, respectively) but also in common cold (55% and 12%, respectively), with plain X-ray predominantly being carried out by PCPs, and CT scan by ORLs. These practices were not related to suspected complications since the frequency of symptoms suggesting complications were very low (0.4% in common cold and 1.5% in postviral ARS).

Although VAS has been validated to assess CRS severity[1, 25, 26], our study has been the first to use it to assess ARS severity. Interestingly, VAS score was similar in both viral and postviral ARS suggesting that disease severity is not associated with the duration of disease. Patients with severe ARS have more smell loss, more facial pain, and more impact on quality of life than patients with

moderate and mild ARS. Moreover, plane X-Ray was more often indicated, and antibiotics more generally prescribed in patients with severe ARS. On the other hand, the presence of symptoms linked to complications was not different between severity groups. Previous studies have reported the impact of ARS on quality of life and its improvement with intranasal corticosteroids[37] or antibiotics[14] using SNOT-20 and SNOT-16, respectively. In our study, postviral ARS had a higher impact on quality of life than common cold but, in both groups, QoL improved and reached normal values no matter the treatment used for 2-4 weeks.

Although guidelines suggest that a diagnosis of bacterial ARS should be considered in patients with fever, severe unilateral pain, purulent rhinorrea, and double sickening[38], there are real difficulties to differentiate between postviral and bacterial ARS. Several studies have reported an abuse of antibiotic prescriptions by PCPs. Dutch PCPs prescribed antibiotics in 34% of patients with moderate ARS[39] while US PCPs did so in 82.3% of ARS cases[40]. In addition, ARS was behind 3.9% of all diagnoses with antibiotic prescription performed by PCPs[41]. In our study, Spanish physicians prescribed antibiotics in most of the ARS cases either in common cold (62%) or in postviral ARS (76%). However, not only PCPs but also ORLs abused antibiotic prescription (53% and 39% respectively). A potential explanation for this could be that PCPs may consider the term “sinusitis” as synonym of bacterial ARS instead of being considered as an inflammatory condition. [42]

Current guidelines[1,37] and recent systematic reviews[20, 43] recommend the use

of oral antibiotics in combination with intranasal corticosteroids only in severe bacterial ARS or in complications. Yet, there are no indications for cases of mild to moderate non-complicated ARS. The potential benefit of antibiotics in treating ARS should be contrasted with the potential of inducing antibiotic resistance and the very low incidence of serious complications.[19,20] Many recent studies have addressed the high costs of antibiotic resistance.[41] Kraker et al.[44] calculated the cost related to *Staphyloccocus aureus* and *Escherichia coli* infections and their antibiotic resistance in Europe resulting in 8,000 deaths and 62 million Euros for 2007. Surprisingly, the incidence of infections by resistant bacteria was higher in countries with high use (i.e. Portugal) compared to those with lower use (i.e. Iceland or Norway) of antibiotics. Similarly, Carter et al.[45] calculated the cost of infections produced by pan-drug-resistant gram negative bacteria in the UK in an estimated 79,000 deaths over a 20-year period. Concerning the role of antibiotics on preventing complications, Babar-Craig et al.[46] reported that complications requiring surgical intervention were similar in patients receiving antibiotic treatment or not. In the Netherlands, Hansen et al.[10] reported a very low rate of ARS complications in both children (1:12,000) and adult (1:32,000) patients which suggested antibiotic treatment did not prevent complications. In our study, the frequency of symptoms suggesting complications was totally independent of the prescribed medication.

Current guidelines[1] and systematic reviews [18,47] recommend the use of intranasal corticosteroids (INS) in moderate (monotherapy) and severe (in combination with antibiotics) ARS. Dolor et al.[17] firstly described that the addition of INS (fluticasone propionate) to antibiotic treatment improved clinical

success rates and accelerated recovery. Further studies demonstrated the superiority of INS (mometasone furoate) in monotherapy over amoxicillin to improve nasal symptoms[48,49] and QoL[37] in patients with moderate non-complicated ARS. In common cold however INS are not related to better cure rates or symptom relieve[50]. In our study, Spanish physicians prescribe INS in two out of five (38%) patients with common cold and in one out of two (54%) patients with postviral ARS, with INS prescription being associated with a longer duration of the disease. As long as the present study is a real life study, a cause-effect relationship cannot be stated (see the limitations of the study at the end of this section), since physicians may reserve INS treatment for cases with more prolonged disease. Some studies have described the efficacy of herbal medicines such as Myrtol,[51] Pelargonium sidoides,[52], and recently BNO 1016[53]. In 2012, Pfaar et al.,[54] reported that CE added-on to antibiotics reached a better symptom control of ARS compared to placebo. In consequence, EPOS guidelines recommended their use in adult ARS[1]. A recent meta-analysis by Kock et al.[24] has confirmed the efficacy of some herbal compounds such as EPs 7630, myrtol, BNO 101, BNO 1016, *Cyclamen europaeum (CE),* and Esberitox. In the present study, an association was found between the use of *CE* and a shorter disease duration suggesting *CE* be accepted by physicians as a treatment choice for ARS. In 2011 Wang et al.[27] published a study reporting a huge amount of medications prescribed in Asia to treat mild ARS (common cold). Over 80% of GPs and ENTs prescribed at least one medication in ARS, with antihistamines (39.2%) and nasal decongestants (33.6%) being among the medications most frequently prescribed. Despite the fact that antihistamines and mucolytics have not shown any benefit on treating

ARS, and are not recommended by international guidelines[1], physicians, and especially PCPs but also ENT specialists, in our study regularly prescribed antihistamines (26%) and mucolytics (45%) to ARS patients.

Weaknesses and Strengths

As with all epidemiological studies, the PROSINUS survey may have some weaknesses. 1) The study population cannot be considered a random sample since there was no control over which patients received specific medications, or in which patients diagnostic tools were performed. We have attempted to address this by estimating regression models adjusted for the RSA type and severity level at Visit 1. In addition, the results have been interpreted in terms of association, avoiding any interpretation in terms of causality. 2) The management performed by PCPs and ORLs cannot directly be compared since they were not parallel but consecutive groups, with the same patients but assessed at different times. In addition, some unmet needs were identified in the study: clear validated criteria to define bacterial ARS, physicians' criteria to prescribing antibiotics. On the other hand our strengths are: 1) the high number of included patients, and that EPOS criteria were followed for inclusion criteria and to classify our patient's population; and 2) the study is a real life and prospective providing a real approach of physician behaviour in their daily clinical practice concerning the management of disease.

CONCLUSIONS

To summarize our findings, we can conclude that despite the fact that consensus guidelines on ARS management have existed for more than a decade, a lot of diagnostic tools are still performed unnecessarily, and a lot of non-recommended medications are prescribed to treat a disease that is mostly self-limited. There is an important unmet need to educate physicians as much as policymakers to manage ARS following evidence-based clinical practice guideline recommendations. It has been proved that the education is effective to reduce antibiotic prescriptions for respiratory tract infections[55] and ARS[56]. We found an overuse of diagnostic tools and prescribed medications but, in addition to the burden and mortality induced by antibiotic resistance due to antibiotic abuse, the associated direct and indirect costs remain to be analysed.

SUMMARIZING BOX:

It is already known that:

- ARS diagnosis is clinical, and imaging tests are not routinely needed.
- ARS is mostly a self-limited disease independent of the treatment used, and the use of antibiotics is not necessary to treat non-complicated ARS.
- The inadequate use of antibiotics is related to a high incidence of antibiotic resistance which has implications for increased socio-sanitary costs and the number of deaths caused by resistant bacteria infections.

This study reports that:

- The physicians (PCPs and ORLS) recommend a high number of non-indicated diagnostic tools and medications.
- The duration of the disease is independent of the use of antibiotics.

• The incidence of symptoms linked to complicated ARS is independent of the use of antibiotics.

ACKNOWLEDGEMENTS

To all centres and specialists in otolaryngology from Spain who participated in the PROSINUS study.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; JM is or has been member of national and international scientific advisory boards (consulting), received fees for lectures, and grants for research projects from ALK-Abelló, FAES, Genentech-Roche, GSK, Hartington Pharmaceuticals, MEDA Pharma, Menarini, MSD, Novartis, Sanofi-Genzyme-Regeneron, UCB, and Uriach Group. No other relationships or activities that could appear to have influenced the submitted work.

The manuscript is an honest, accurate, and transparent account of the study being reported, and no important aspects of the study have been omitted.

FUNDING

The PROSINUS study was partially sponsored by an unrestricted research grant from Hartington Pharmaceuticals.

CONTRIBUTORS

FJ is the guarantor of the study, and has contributed with the conception and design of the study, literature search, acquisition of data, analysis and interpretation of data and writing the manuscript.

LQ has contributed with the study design, acquisition of data, statistical analysis

and interpretation of data and drafting the manuscript and approving its final version.

IA has contributed through literature research, interpretation of data and by drafting the manuscript and approving its final version.

JM has contributed with the conception and design of the study, acquisition of data, analysis and interpretation of data and a critical reading of the manuscript and approving its final version.

FIGURE LEGENDS

Figure 1. Flow-chart of participants in the PROSINUS study. Two phenotypes for acute (ARS) and one for chronic (CRS) rhinosinusitis were analysed: patients with viral ARS / common cold (36%), postviral ARS (63%), and chronic rhinosinusitis (1%).

Figure 2. Frequency of symptoms in acute rhinosinusitis patients. Bars represent the frequency (%) of individual sinonasal symptoms in each level of severity for both viral and postviral acute rhinosinusitis (ARS). Reported frequency of symptoms was always higher in the highest severity level. *, $p<0.05$; NS, not significant.

Figure 3. Diagnostic tools performed in acute rhinosinusitis patients. Percentage of patients undergoing different diagnostic tools, for both viral and postviral acute rhinosinusitis, recommended by either Primary Care Physicians or Otorhinolaryngologists. *, $p<0.05$; NS, not significant.

Figure 4. Prescribed medications in acute rhinosinusitis patients. Percentage of patients being treated with different medications, for both viral and postviral acute rhinosinusitis (ARS), prescribed by either Primary Care Physicians or Otorhinolaryngologists. *, $p<0.05$; NS, not significant.

Figure 5. Quality of life (SNOT-16) in acute rhinosinusitis patients. Changes in the individual values (solid lines) and in the average values of each

group (dashed lines). At baseline, SNOT-16 score was more affected (*, $p<0.05$) in postviral than in viral acute rhinosinusitis (ARS). SNOT-16 score significantly improved (‡, $p<0.05$) after disease resolution with no differences between both ARS phenotypes.

Table 1. Socio-demographic characteristics of acute rhinosinusitis (ARS) study populat

Demographic characteristics		Viral ARS (N=494)	Postviral ARS (N=857)	Total ARS (N=1,351)	p-value
Age [1]		42.2 ±14.3 (424)	42.6±14.0 (761)	42.4±14.1 (1185)	0.6871 [2]
Gender [3]	Men	234/471 (50)	375/821 (46)	609/1,292 (47)	0.1651 [4]
Area of residence [3]	Rural	23 (5)	52 (6)	75 (6)	0.1094 [4]
	Semi-rural	52 (11)	120 (15)	172 (13)	
	Urban	392 (84)	653 (79)	1,045 (81)	
	Total	467 (100)	825 (100)	1,292 (100)	
Place of residence [3]	With family / couple	440 (89)	748 (88)	1,188 (88)	0.4976 [5]
	Single	44 (9)	91 (11)	135 (10)	
	Institution / residence	4 (1)	3 (0)	7 (1)	
	Shared housing	6 (1)	11 (1)	17 (1)	
	Total	494 (100)	853 (100)	1,347 (100)	
Education level [3]	No / unfinished education	45 (9)	84 (10)	129 (10)	0.2855 [4]
	Primary / secondary education	219 (45)	415 (49)	634 (47)	
	College / higher education	225 (46)	355 (42)	580 (43)	
	Total	489 (100)	854 (100)	1,343 (100)	
Daily activity [3]	Well air-conditioned enclosure	332 (68)	534 (63)	866 (65)	0.0092 [4]
	Poorly air-conditioned enclosure	37 (8)	113 (13)	150 (11)	
	Outdoors	38 (8)	54 (6)	92 (7)	
	Unemployed	78 (16)	146 (17)	224 (17)	
	Total	485 (100)	847 (100)	1,332(100)	
Well heated home [3]		449/477 (94)	751/823 (91)	1,200/1,300 (92)	0.0605 [4]
Airy home [3]		395/415 (95)	731/757 (97)	1,126/1,172 (96)	0.2430 [4]

1, Arithmetic mean±SD (n)
2, Student t-test
3, n (%)
4, Chi-squared test
5, Fisher's exact test

Table 2. Frequency of symptoms in viral/postviral acute rhinosinusitis (ARS)

	Viral ARS (N=494)	Postviral ARS (N=857)	p-value
Nasal obstruction [1]	481/493 (98)	829/857 (97)	0.3847[2]
Rhinorrea [1]	464/490 (95)	800/854 (94)	0.4482[2]
Facial pressure/pain [1]	370/485 (76)	653/848 (77)	0.7659[2]
Loss of smell [1]	275/470 (59)	533/847 (63)	0.1148[2]

1, number of cases and proportion within group (%)
2, Chi-squared test

Table 3. Frecuency of recommended combined medications in acute rhinosinusitis (ARS).

Recommended medications		Viral ARS (N=494)	Postviral ARS (N=857)	Total ARS (N=1,351)	p-value
No treatment [1]		27 (5)	20 (2)	47 (3)	0.0025 [2]
Antibiotic [1]	AB (total)	308 (62)	648 (76)	956 (71)	< 0.0001 [2]
	AB alone	13 (3)	6 (1)	19 (1)	0.0037 [2]
	AB in combination (except with CS)	137 (28)	261 (30)	398 (29)	0.2905 [2]
Intranasal CS [1]	Topical CS (total)	188 (38)	463 (54)	651 (48)	< 0.0001 [2]
	Topical CS alone	1 (0)	1 (0)	2 (0)	1.0000 [3]
	Topical CS in combination (except with Ab)	29 (6)	81 (9)	110 (8)	0.0204 [2]
Phytoteraphy [1]	Phytoteraphy (total)	205 (41)	391 (46)	596 (44)	0.1413 [2]
	Phytoteraphy alone	20 (4)	9 (1)	29 (2)	0.0002 [2]
	Phytoteraphy in combination (except with AB or CS)	39 (8)	46 (5)	85 (6)	0.0654 [2]
Antibiotic + intranasal CS [1]	AB + topical steroids alone	12 (2)	4 (0)	16 (1)	0.0013 [2]
	AB + topical CS in combination	146 (30)	377 (44)	523 (39)	< 0.0001 [2]
Saline solutions [1]	Saline solutions (total)	197 (40)	462 (54)	659 (49)	< 0.0001 [2]
	Saline solutions alone	9 (2)	4 (0)	13 (1)	0.0193 [3]
	Saline solutions in combination	188 (38)	458 (53)	646 (48)	< 0.0001 [2]
Other combinations without AB, intranasal CS or phytotherapy [1]		70 (14)	52 (6)	122 (9)	< 0.0001 [2]
Mucolitics [1]		235 (48)	515 (60)	750 (56)	< 0.0001 [2]
Antihistamines [1]		154 (31)	396 (46)	550 (41)	< 0.0001 [2]
Nasal decongestants [1]		190 (38)	412 (48)	602 (45)	0.0006 [2]

1 number of cases and proportion within group (%)
2 Chi-squared test
3 Fisher's exact test
AB, antibiotic; ARS, acute rhinosinusitis; CS, corticosteroids.

Table 4. Frequency of unusual symptoms and symptoms suggesting a complication of acute rhinosinusitis (ARS).

			Total ARS (N=1,351)	Viral ARS (N=494)	Postviral ARS (N=857)	p-value
Unusual symptoms (consider different diagnosis) [1]	Total		49 (3.6)	12 (2.4)	37 (4.3)	0.0738 [2]
	Unilateral symptoms		8 (0.6)	2 (0.4)	6 (0.7)	0.7179
	Bleeding		30 (2.2)	8 (1.6)	22 (2.6)	0.2549
	Crusts		10 (0.7)	2 (0.4)	8 (0.9)	0.3419
	Lacrimation and conjunctiva hyperaemia		13 (1)	3 (0.6)	10 (1.2)	0.3950
	Cacosmia		2 (0.1)	0 (0)	2 (0.2)	0.5358
Symptoms suggesting a complication [1]	Total		15 (1.1)	2 (0.4)	13 (1.5)	0.0603 [2]
	Orbital symptoms	Total	9 (0.7)	1 (0.2)	8 (0.9)	0.1673 [3]
		Palpebral oedema	6 (0.4)	1 (0.2)	5 (0.6)	0.4246
		Exophthalmos	0 (0)	0 (0)	0 (0)	_
		Diplopia	1 (0.1)	0 (0)	1 (0.1)	1.0000
		Ocular pain	5 (0.4)	0 (0)	5 (0.6)	0.1652
		Decrease of visual acuity	2 (0.1)	0 (0)	2 (0.2)	0.5358
		Other orbital symptoms	2 (0.1)	0 (0)	2 (0.2)	0.5358
	Frontal symptoms	Total	9 (1.1)	1 (0.2)	8 (0.9)	0.1673 [3]
		Intense frontal pain	9 (0.7)	1 (0.2)	8 (0.9)	0.1673
		Frontal oedema	1 (0.1)	0 (0)	1 (0.1)	1.0000
	Neurologic symptoms		0 (0)	0 (0)	0 (0)	_
	Systemic symptoms		0 (0)	0 (0)	0 (0)	_

1 number of cases and proportion within group (%)
2 Chi-squared test
3 Fisher's exact test

Table 5. Risk factors for a viral leading to a postviral acute rhinosinusitis (ARS).

		Viral ARS (N=237)	Postviral ARS (N=452)	Total ARS (N=689)	OR	95% CI	p
Age [1]		42.3±14.3 (237)	42.2±13.7 (452)	42.3±13.9 (689)	1.00	(0.99; 1.01)	0.9104
Gender [2]	Men	111 (47)	208 (46)	319 (46)	1		0.8380
	Women	126 (53)	244 (54)	370 (54)	1.03	(0.75; 1.42)	
	Total	237 (100)	452 (100)	689 (100)			
Area of residence [2]	Rural	12 (5)	20 (4)	32 (5)	1		0.5672
	Semi-rural	26 (11)	62 (14)	88 (13)	1.43	(0.61; 3.35)	
	Urban	199 (84)	370 (82)	569 (83)	1.12	(0.53; 2.33)	
	Total	237 (100)	452 (100)	689 (100)			
Place of residence [2]	With family / couple	210 (89)	399 (88)	609 (88)	1		
	Alone	23 (10)	48 (11)	71 (10)	1.10	(0.65; 1.86)	0.9064
	Institution / residence	1 (0)	1 (0)	2 (0)	0.53	(0.03; 8.46)	
	Shared housing	3 (1)	4 (1%)	7 (1%)	0.70	(0.16; 3.16)	
	Total	237 (100)	452 (100)	689 (100)			
Education level [2]	No / unfinished education	13 (5)	30 (7)	43 (6)	1		0.4829
	Primary / secondary education	106 (4)	218 (48)	324 (47)	0.89	(0.45; 1.78)	
	College / higher education	118 (50)	204 (45)	322 (47)	0.75	(0.38; 1.49)	
	Total	237 (100)	452 (100)	689 (100)			
Daily activity [2]	Well air-conditioned enclosure	171 (72)	302 (67)	473 (69%)	1		0.0323
	Bad air-conditioned enclosure	16 (7)	64 (14)	80 (12)	2.26	(1.27; 4.04)	
	Outdoors	17 (7)	23 (5)	40 (6)	0.77	(0.40; 1.47)	
	Unamployed	33 (14)	63 (14)	96 (14)	1.08	(0.68; 1.71)	
	Total	237 (100)	452 (100)	689 (100)			
Well heated home [2]		221 / 237 (93)	407 / 452 (90)	628 / 689 (91)	0.65	(0.36; 1.19)	0.1620
Airy home [2]		229 / 237 (97)	440 / 452 (97)	669 / 689 (97)	1.28	(0.52; 3.18)	0.5933

1 Arithmetic Mean ± SD (n)
2 number of cases and proportion within group (%)

BIBLIOGRAPHY

1. Fokkens WJ, Lund VJ, Mullol J, et al. The European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinology* 2012;50(Suppl 23):1-299

2. Klossek J, Mesbah K. Presentation and treatment of acute maxillary sinusitis in general practice: A French observational study. *Rhinology* 2011;49-1:84-9.

3. Stjärne P, Odebäck P, Ställberg B, et al. High costs and burden of illness in acute rhinosinusitis: real-life treatment patterns and outcomes in Swedish primary care. *Prim Care Respir J* 2012;21:174-9

4. Passioti M, Maggina P, Megremis S, et al. The common cold: potential for future prevention or cure. *Curr Allergy Asthma Rep* 2014;14:413.

5. Van Kempen M. An update on the pathophysiology of rhinovirus upper respiratory tract infections. *Rhinology*1999;37:97-103.

6. Berg O, Carenfelt C, Rystedt G, Anggard A. Occurrence of asymptomatic sinusitis in common cold and other acute ENT-infections. *Rhinology* 1986;24:223-5.

7. Smith SS, Ference EH, Evans CT, et al. The prevalence of bacterial infection in acute rhinosinusitis: a Systematic review and meta-analysis. *Laryngoscope 2015*;125:57-69.

8. Turner RB. Epidemiology, pathogenesis and treatment of the common cold. *Ann Allergy Asthma Immunol* 1997;78:531-40.

9. Oskarsson JP, Halldorsson S. Anevaluation of diagnosis and treatment of acute sinusitis at three healthcare centers. *Laeknabladid* 2010;96:531-5.

10. Hansen FS, Hoffmans R, Georgalas C, et al. Complications of acute rhinosinusitis in The Netherlands. *Fam Pract* 2012;29:147-53.

11. Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in Rhinology EAACI position paper. *Clin Transl Allergy* 2011;1:2.

12. Ebell MH, McKay B, Guilbault R, et al. Diagnosis of acute rhinosinusitis in primary care: a systematic review of test accuracy. *Br J Gen Pract* 2016;66:e612-32.

13. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev* 2008;16:CD000243.

14. Garbutt JM, Banister C, Spitznagel E, et al. Amoxicillin for acute rhinosinusitis: a randomized controlled trial. *JAMA* 2012;307:685-92.

15. Ahovuo-Saloranta A, Rautakorpi UM, Borisenko OV, et al. Antibiotics for acute maxillary sinusitis in adults. *Cochrane Database Syst Rev* 2014;11:CD000243.

16. Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.

17. Dolor RJ, Witsell DL, Hellkamp AS, et al. Ceftin and Flonase for Sinusitis (CAFFS) Investigators. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. *JAMA* 2001;286:3097-105.

18. Hayward G, Heneghan C, Perera R, et al. Intranasal corticosteroids in management of acute sinusitis: a systematic review and meta-analysis. *Ann Fam Med* 2012;10:241-9.

19. Smith SR, Montgomery LG, Williams JW Jr. Treatment of mild to moderate sinusitis. *Arch Intern Med* 2012;172:510-3.

20. Lemiengre MB, van Driel ML, Merenstein D, et al. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. *Cochrane Database Syst Rev* 2012;10:CD006089.

21. Passali GC, et al. A prospective open-label study to assess the efficacy and safety of a herbal medicinal product (Sinupret) in patients with acute rhinosinusitis. *ORL J Otorhinolaryngol Relat Spec* 2015;77:27-32.

22. Mullol J, Crespo C, Carré C, Brosa M. *Pharmacoeconomics of Cyclamen europaeum* in the management of acute rhinosinusitis. *Laryngoscope* 2013;123:2620-5.

23. Ponikau JU, Hamilos DL, Barreto A, et al. An exploratory trial of *Cyclamen europaeum* extract for acute rhinosinusitis. *Laryngoscope* 2012;122(9):1887-92.

24. Koch AK, Klose P, Lauche R, et al. A Systematic Review of Phytotherapy for Acute Rhinosinusitis. *Forsch Komplementmed* 2016;23:165-9.

25. Fokkens W, Lund V, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2007. European Position Paper on Rhinosinusitis and Nasal Polyps group. *Rhinology* 2007;Suppl 20:1-136.

26. Lim M, Lew-Gor S, Darby Y, et al. The relationship between subjective assessment instruments in chronic rhinosinusitis. *Rhinology* 2007;45:144-7

27. Wang DY, Wardani RS, Singh K, et al. A survey on the management of acute rhinosinusitis among Asian physicians. *Rhinology* 2011;49:264-71.

28. Van Gageldonk-Lafeber AB, van der Sande MA, Heijnen ML, et al. Risk factors for acute respiratory tract infections in general practitioner patients in The Netherlands: a case-control study. *BMC Infect Dis* 2007;7:35.

29. Van Gageldonk-Lafeber AB, Heijnen ML, Bartelds AI, et al. A case-control study of acute respiratory tract infection in general practice patients in The Netherlands. *Clin Infect Dis* 2005;4:490-7.

30. Schatz M, Zeiger RS, Chen W, et al. The burden of rhinitis in a managed care organization. *Ann Allergy Asthma Immunol* 2008;101:240-7.

31. Zuskin E, Mustajbegovic J, Schachter EN, et al. Respiratory findings in mail carriers. *Int Arch Occup Environ Health* 2000;73:136-43.

32. Bonham GS, Wilson RW. Children's health in families with cigarette smokers. *Am J Public Health* 1981;71:290-3.

33. Jonas I, Mann W. Misleading x-ray diagnosis due to maxillary sinus asymmetries (author's transl). *Laryngol Rhinol Otol (Stuttg)* 1976;55:905-13.

34. McAlister WH, Lusk R, Muntz HR.Comparison of plain radiographs and coronal CT scans in infants and children with recurrent sinusitis. *AJR Am J Roentgen*ol 1989;153:1259-64.

35. Bird J, Biggs TC, Thomas M, Salib RJ. Adult acute rhinosinusitis. *BMJ* 2013;346:f2687.

36. Gwaltney JM, Phillis CD, Miller RD, et al. Computed tomographic study of the common cold. *N Eng J Med* 1994;330:25-30.

37. Bachert C, Meltzer EO. Effect of mometasone furoate nasal spray on quality of life of patients with acute rhinosinusitis. *Rhinology* 2007;45:190-6.

38. Fokkens WJ, Hoffmans R, Thomas M. Avoid prescribing antibiotics in acute rhinosinusitis.. *BMJ*. 2014;17:349.

39. Hoffmans R, Schermer T, van WC, et al. Management of rhinosinusitis in Dutch general practice. *Prim Care Respir J* 2011;20:64-70.

40. Smith SS, Kern RC, Chandra RK, Tan BK, Evans CT. Variations in antibiotic prescribing of acute rhinosinusitis in United States ambulatory settings. *Otolaryngol Head Neck Surg* 2013;148(5):852-9.

41. Smith SS, Evans CT, Tan BK, Chandra RK, Smith SB, Kern RC. National

burden of antibiotic use for adult rhinosinusitis. *J Allergy Clin Immunol* 2013;132(5):1230-2.

42. Steurer J, Held U, Bachmann LM, et al. Clinical diagnosis of acute bacterial rhinosinusitis, typical of experts. *J Eval Clin Pract* 2009;15:614-9.

43. Sng WJ, Wang DY. Efficacy and side effects of antibiotics in the treatment of acute rhinosinusitis: a systematic review. *Rhinology* 2015;53:3-9.

44. de Kraker ME, Davey PG, Grundmann H.Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med* 2011;8(10):e1001104.

45. Carter D, Charlett A, Conti S, et al. A Risk Assessment of Antibiotic Pan-Drug-Resistance in the UK: Bayesian analysis of an expert elicitation study. *Antibiotics (Basel)* 2017;7:6(1):E9.

46. Babar-Craig H, Gupta Y, Lund VJ. British Rhinological Society audit of the role of antibiotics in complications of acute rhinosinusitis: a national prospective audit. *Rhinology* 2010;48:344-7.

47. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. *Cochrane Database Syst Rev* 2009;(4):CD005149.

48. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol* 2005;116:1289-95.

49. Keith PK, Dymek A, Pfaar O, et al. Fluticasone furoate nasal spray reduces symptoms of uncomplicated acute rhinosinusitis: a randomised placebo-controlled study. *Prim Care Respir J* 2012;21:267-75.

50. 49. Hayward G, Thompson MJ, Perera R, et al. Corticosteroids for the common cold. *Cochrane Database Syst Rev* 2012;15:CD008116.

51. Federspil P, Wulkow R, Zimmermann T. Effects of standardized Myrtol in therapy of acute sinusitis--results of a double-blind, randomized multicenter study compared wi th placebo. *Laryngorhinootologie* 1997;76:23-7.

52. Timmer A, Gunther J, Rucker G, et al. Pelargonium sidoides extract for acute respiratory tract infections. *Cochrane Database Syst Rev* 2008;3:CD006323.

53. Jund R, Mondigler M, Stammer H, et al. Herbal drug BNO 1016 is safe and effective in the treatment of acute viral rhinosinusitis. *Acta Otolaryngol* 2015;135:42-50.

54. Pfaar O, Mullol J, Anders C, et al. Cyclamen europaeum nasal spray, a novel phytotherapeutic product for the management of acute rhinosinusitis: a randomized double-blind, placebo-controlled trial. *Rhinology* 2012;50:37-44.

55. Little P, Stuart B, Francis N, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013; 382(9899):1175-82.

56. Gjelstad S, Høye S, Straand J, et al. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). *BMJ* 2013;347:f4403.

Figure 1

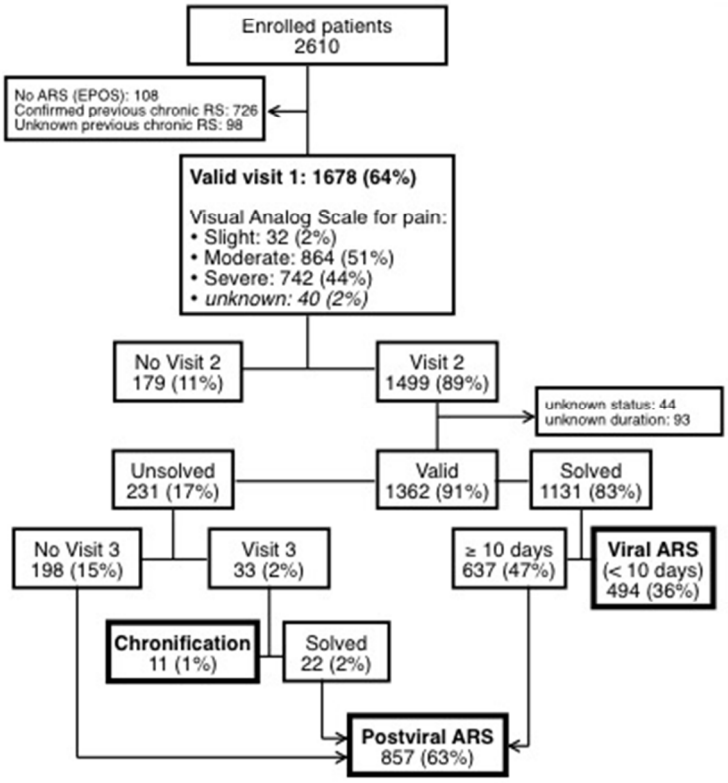

Figure 1

191x167mm (72 x 72 DPI)

Figure 2

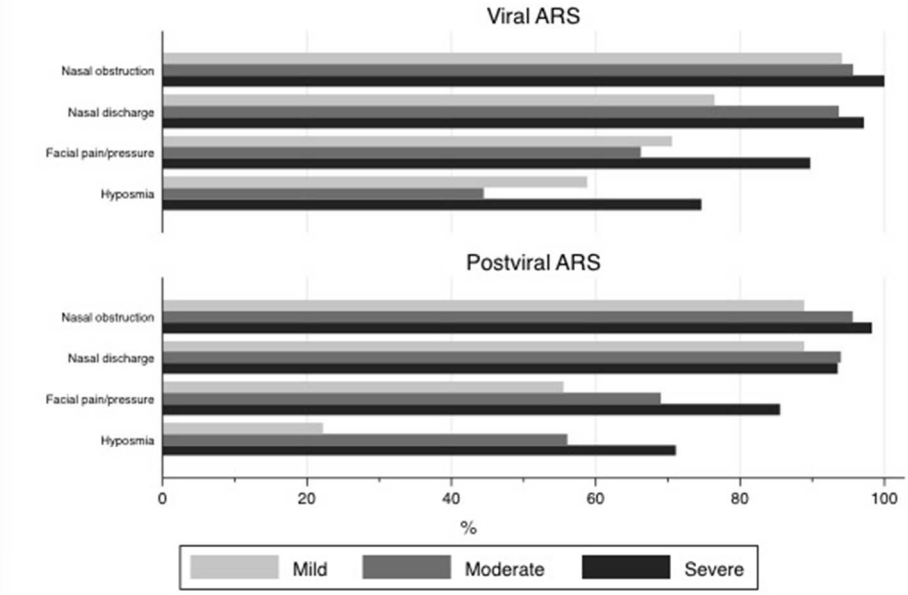

Figure 2

224x181mm (72 x 72 DPI)

Figure 3

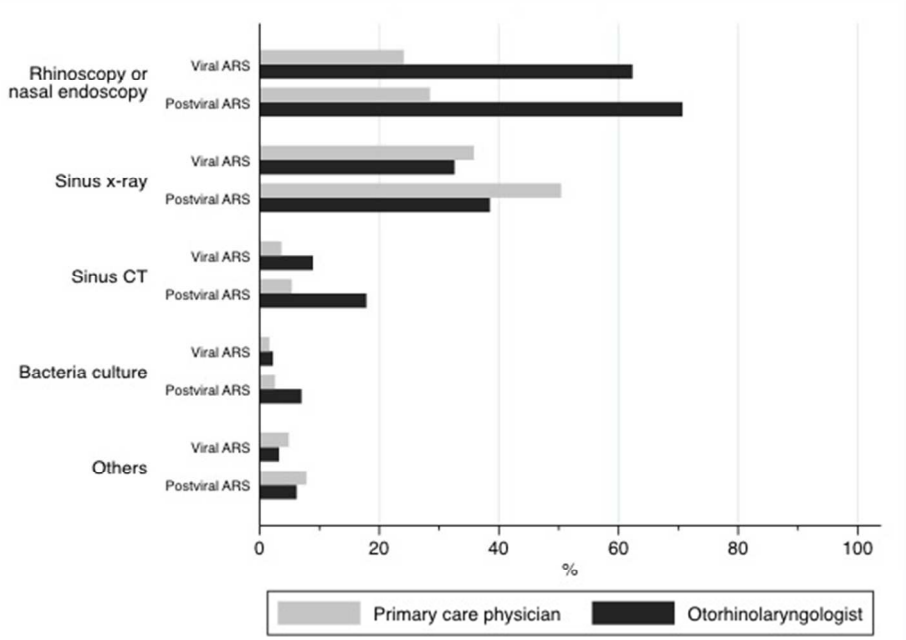

Figure 3

228x179mm (72 x 72 DPI)

Figure 4

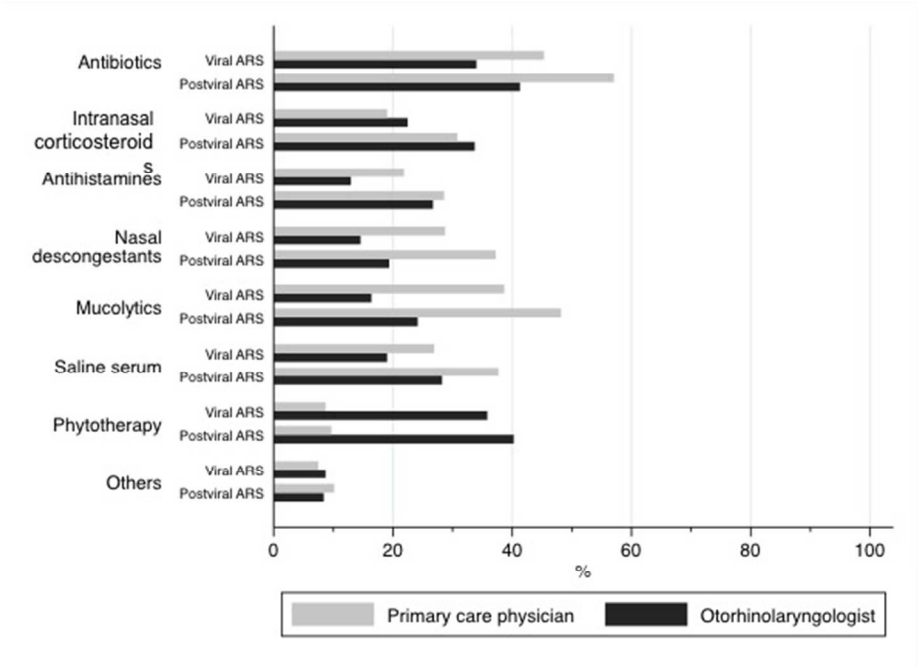

Figure 4

228x182mm (72 x 72 DPI)

Figure 5

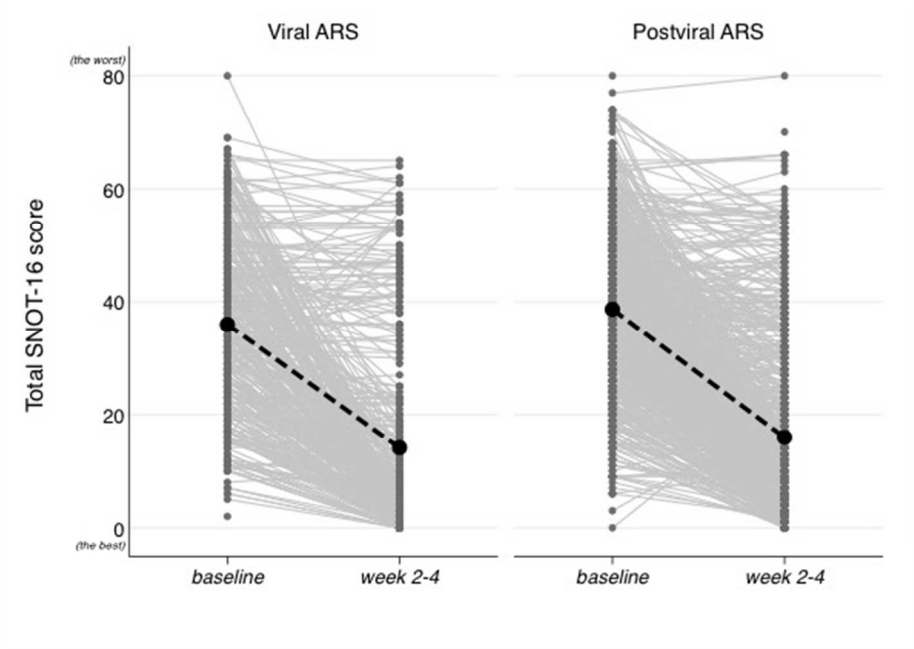

Figure 5

230x171mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract pag 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found pag 2-3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported pag 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses pag 5
Methods		
Study design	4	Present key elements of study design early in the paper pag 6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection pag 6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up pag 6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable pag 6-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group pag 7-11
Bias	9	Describe any efforts to address potential sources of bias pag 23
Study size	10	Explain how the study size was arrived at pag 10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why pag 10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding pag 10-11
		(*b*) Describe any methods used to examine subgroups and interactions pag 10-11
		(*c*) Explain how missing data were addressed The results are derived from a complete case analysis (CC), under the assumption that the missing pattern was Missing At Random (MAR). According to the results from Mukaka et al.[1] recently published in Trials (2016) 17:341 for MAR outcomes, CC method estimates generally remain unbiased and achieve precision similar to or better than Multiple Imputation (MI) methods. However, we would like to point out that we also estimated the multivariate models after MI and obtained very similar results. 1.Rubin, D.B., 1987. Multiple Imputation for Nonresponse in Surveys. John Wiley and Sons, New York.
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses We don't perform any sensitivity analysis. Instead of that we perform the analysis with Multiple Imputation (MI) methods the missing imputation to prove that the results were similar than a complete case analysis.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed pag 12
		(b) Give reasons for non-participation at each stage The flow chart (Fig 1) include the reasons for non-participation at each stage.

		(c) Consider use of a flow diagram Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders pag 12
		(b) Indicate number of participants with missing data for each variable of interest Each table reports the number of participants with data for each variable (Tables 1-5)
		(c) Summarise follow-up time (eg, average and total amount) pag 12
Outcome data	15*	Report numbers of outcome events or summary measures over time pag 12-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included pag 12-17
		(*b*) Report category boundaries when continuous variables were categorized The VAS score to assess severity was categorized as mild, moderate or severe according the paper published by Lim et al. Rhinology 2007. No other continuous variables were assessed.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. We don't use relative risk
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses pag 12-17
Discussion		
Key results	18	Summarise key results with reference to study objectives pag 18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias pag 23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence pag 18-24
Generalisability	21	Discuss the generalisability (external validity) of the study results pag 23
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based pag 25-26

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Overuse of diagnostic tools and medications in acute rhinosinusitis in Spain: a population based study (the PROSINUS study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018788.R1
Article Type:	Research
Date Submitted by the Author:	16-Oct-2017
Complete List of Authors:	Jaume Monroig, Francesca; Hospital Clinic, Universitat de Barcelona, Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Immunoal.lèrgia Respiratòria Clínica i Experimental Quintó, Llorenç; Institut de Salut Global de Barcelona (ISGlobal) de Recerca en Salut Internacional de Barcelona (CRESIB); Centro de Investigación Biomédica En Red en Epidemiología y Salud Pública (CIBERESP). Alobid, Isam; Hospital Clinic, Universitat de Barcelona, Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Immunoal.lèrgia Respiratòria Clínica i Experimental Mullol i Miret, Joaquim; Hospital Clínic, Universitat de Barcelona, Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Immunoal.lèrgia Respiratòria Clínica i Experimental
Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Infectious diseases, Medical management
Keywords:	acute rhinosinusitis, common cold, antibiotics, intranasal corticosteroids, phytotherapy, PROSINUS

Overuse of diagnostic tools and medications in acute rhinosinusitis in Spain: a population based study (the PROSINUS study)

Francesca Jaume Monroig, research fellow,[1,2] **Llorenç Quintó**, statistician,[4,5] **Isam Alobid**, professor of otorhinolaryngology,[1,2,3] **Joaquim Mullol i Miret**, professor of research.[1,2,3]

1) Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia, Hospital Clínic, Universitat de Barcelona, Barcelona, Catalonia, Spain; 2) Immunoal.lèrgia Respiratòria Clínica i Experimental, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain; 3) Centro de Investigación Biomédica En Red en Enfermedades Respiratorias (CIBERES); 4) Institut de Salut Global de Barcelona (ISGlobal) de Recerca en Salut Internacional de Barcelona (CRESIB), Barcelona, Catalonia, Spain; 5) Centro de Investigación Biomédica En Red en Epidemiología y Salud Pública (CIBERESP).

CORRESPONDING AUTHOR:

Joaquim Mullol i Miret, MD, PhD. Unitat Rinologia i Clínica de l'Olfacte, ENT Department, Hospital Clínic, IDIBAPS, Villarroel 170, 08036 Barcelona, Catalonia, Spain. Tel: +34 932 279 872, Fax: +34 932 279 813, e-mail: jmullol@clinic.cat

ABSTRACT

Objectives. Acute rhinosinusitis (ARS) has a high incidence. Diagnosis is clinical. Evolution mostly self-limited. The aim of this study was to describe socio-demographic characteristics, and use of diagnostic tools and medications in patients with ARS.

Design. Prospective observational study in real life clinical practice.

Setting. Patients with clinical diagnosis of ARS (N=2,610) were included from ENT clinics in Spain. A second visit at resolution was done.

Participants. Patients were classified according to the duration of symptoms: viral ARS (≤10days), postviral ARS (>10days, ≤12weeks), chronic RS (>12weeks).

Main outcome measures. Socio-demographic characteristics, symptoms, disease severity, quality of life (SNOT-16), used diagnostic tools and medications, and the management performed by Primary Care Physicians (PCPs) and by Otorhinolaryngologists (ORLs) was assessed.

Results. Patients were classified as viral (36%) and postviral (63%) ARS, and 1% as chronic. Working in a poorly air-conditioned environment was a risk factor [Odds Ratio (OR)=2.26 (1.27, 4.04)] in developing postviral ARS. A higher number of diagnostic tools (rhinoscopy/endoscopy 80%vs.70%; plain X-ray 70%vs.55%; CT scan 22%vs.12%; p-values<0.0001) were performed in postviral than viral cases. PCPs performed more X-rays than ORLs (p<0.0001). Patients, more those with postviral than viral ARS, received a high number of medications (oral antibiotics: 76%vs.62%; intranasal corticosteroids: 54%vs.38%; antihistamines: 46%vs.31%; mucolytic 48%vs.60% (p-

values<0.0001). PCPs prescribed more antibiotics, antihistamines, and mucolytics than ORLs (p-values<0.0068). More patients with postviral than viral ARS reported symptoms of potential complications (1.5%vs.0.4%, p=0.0603). Independently of prescribed medications QoL was more affected in postviral (38.7±14.2 vs. 36.0±15.3, p=0.0031) than viral ARS. ARS resolution was obtained after 6.04 (viral) and 16.55 (postviral) days, with intranasal corticosteroids being associated with longer [OR=1.07 (1.02, 1.12)] and phytotheraphy with shorter [OR=0.95 (0.91, 1.00)] duration.

Conclusions. There is a significant overuse of diagnostic tools and prescribed medications, predominantly oral antibiotics, by PCPs and ORLs, for viral and postviral ARS.

STRENGHTS AND LIMITATIONS:

- Strengths:
  - This is a real life prospective study which provides a real approach of physician behaviour in their daily clinical practice concerning the management of acute rhinosinusitis in Spain.
  - The high number of included patients makes the results highly extensible to the general population.
  - Following EPOS classification criteria makes this study adequate to international guidelines.
- Weaknesses / Limitations:
  - The study population cannot be considered a random sample, so the results have been interpreted in terms of association, avoiding any interpretation in terms of causality.

- The management performed by PCPs and ORLs can not directly be compared as they treat the same patients but in different time of disease.
- Important unmet needs were also identified: lack of validated criteria to diagnose bacterial acute rhinosinusitis and, in consequence, to prescribe antibiotics.

KEYWORDS: acute rhinosinusitis, common cold, antibiotics, intranasal corticosteroids, phytotherapy, PROSINUS.

INTRODUCTION

Rhinosinusitis is an inflammatory process of the paranasal sinuses with high prevalence in clinical practice[1] and a significant impact on quality of life.[2,3] Acute rhinosinusitis (ARS) is mainly an inflammatory disease, usually caused by a viral infection, although other processes such allergic rhinitis, anatomical abnormalities, nasal polyps, tobacco smoke, or nasal decongestant abuse can constitute predisposing factors.[1] Viral ARS (common cold) is usually self-resolved and accounts for most of ARS cases.[4] Postviral ARS occurs as a perpetuation of the inflammatory condition, even when the viral agent has gone.[5] Only a small percentage of the latter (0.5-2%) actually lead to acute bacterial rhinosinusitis (ABRS).[6,7] The incidence of ARS is very high, adults having between two to five common cold episodes per year[8], while the incidence of postviral ARS has been reported to be 3.4 cases per 100 inhabitants/year.[9] Orbital, osseous, or intracranial complications may occur, but their incidence is very low (about 3 cases per million people).[10]

The diagnosis of ARS is based on the clinical history of a sudden onset of nasal symptoms (nasal congestion/obstruction/blockage, rhinorrea/postnasal drip, facial pain/pressure, and/or reduction/loss of smell) supported by physical examination.[1] Microbiological or imaging studies are not required,[11,12], with imaging being indicated when symptoms suggesting complications appear.[1]

The goals of ARS treatment are to provide symptomatic relief, accelerate time of remission, and prevent complications. Although antibiotics have traditionally been the treatment most often indicated for ARS, there is no evidence that antibiotics are significantly better than placebo in viral (common cold) and

postviral ARS[13]. In fact, a number of bacterial ARS cases have been resolved without antibiotics at all.[14,15] Furthermore, the use of antibiotics does not prevent complications.[10] Indeed, their overuse can lead to a number of side effects and to an increase of antibiotic resistance.[16] In the last two decades several studies have demonstrated that the addition of intranasal corticosteroids to antibiotics, or even intranasal corticosteroids in monotherapy, may provide an excellent option to treat postviral ARS.[17;18] Accordingly, European position paper on rhinosinusitis and nasal polyps (EPOS) 2012 recommended symptomatic relievers (analgesics, saline serum, and decongestants) for viral/common cold cases, intranasal corticosteroids for postviral cases, and the addition of oral antibiotic for bacterial/complicated cases or well-established complications.[19,20] Recent studies have shown that selected herbal medicines (phytotherapy) may constitute an additional medical option to treat viral/postviral ARS.[21-24] However, a number of very commonly used medications such as mucolytics, antihistamines, probiotics, or vitamin C have not shown any evidence of efficacy in ARS.[1]

The objectives of the PROSINUS study were: 1st) to describe and compare the diagnostic tools and therapeutic medications used by primary care physicians (PCPs) and Otorhinolaryngologists (ORLs) to manage viral or postviral ARS in Spain, 2nd) to assess the risk factors leading to postviral ARS, and 3rd) to assess the evidence of the efficacy of those medications most often used to decrease disease duration and prevent complications in patients with viral or postviral ARS.

METHODOLOGY

Study design, participants, and setting.

The *"PROspective epidemiological study about the diagnosis and therapeutic management of Acute RhinoSINUsitis in otorhinolaryngology clinics in Spain (PROSINUS study)"* was a prospective, real life, and descriptive study that analysed a cohort of patients (N=2,610) with acute ARS in Spain. Patients recruited by Otorhinolaryngologists (N=284) throughout Spain and classified as suffering from viral (common cold) or postviral ARS based in EPOS criteria. Each ORL represented 9.2±1.8 patients (range 1-11).

To define and classify rhinosinusitis we used the definitions provided by EPOS *(European Position Paper on Rhinosinusitis and Nasal Polyps)* consensus.[25] ARS was clinically defined by a sudden onset of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or anterior/posterior nasal discharge. Additional symptoms could be facial pain/pressure and/or reduction/loss of smell. Three different phenotypes of ARS were defined. Viral ARS (common cold) was defined as the presence of symptoms of rhinosinusitis for less than 10 days, postviral ARS was as symptoms lasting for >10 days and <12 weeks, and chronicity when symptoms lasted for ≥12 weeks.

Inclusion criteria. Patients of both gender, ≥18 years old, who come to see the ORL with symptoms consistent with the clinical diagnosis of viral/postviral ARS according to the EPOS criteria.[25]

Exclusion criteria. Patients with exacerbations of diagnosed CRS, with clinical suspicion of bacterial ARS (severe cases with fever >38ºC or unilateral severe pain), or patients not able to do follow-up visits or with a high risk of dropout.

Study visits. Patients were included between January 2007 and March 2008. Visit 1 was done at inclusion, while visit 2 was done after 2-4 weeks of inclusion. Where patients still had symptoms at visit 2, a visit 3 was performed after 12 weeks of inclusion.

Patient's involvement. Participants were involved in the study on the basis of daily clinical practice. Patients did not participate in the design of the study.

Ethics. The Ethics Committee of our institution *(Comité Ètic de Investigació Clínica de l'Hospital Clínic de Barcelona: CEIC)* approved the study (2006/3305) and all patients signed the informed consent.

Measurements, and Outcomes

At Visit 1, socio-demographic and anthropometric characteristics, duration of symptoms (days), severity of disease, quality of life (SNOT-16), diagnostic tools used, and medications prescribed before inclusion by PCPs were recorded. The general health status prior to and during the disease was also recorded. At Visit 2, the duration of episode (number of days), symptoms addressing potential complications, diagnostic tools used and medications prescribed between visits

1 and 2 by ORLs, severity of disease, and quality of life (SNOT-16) were also recorded. Where Visit 3 was required (based on no resolution at Visit 2), the time of disease resolution or chronification was recorded.

Demographic Characteristics. At Visit 1 the following characteristics were recorded: age (years), gender, area of residence (rural, <2,000 inhabitants; semi-rural, 2,000-10,000 inhabitants; and urban, >10,000 inhabitants), education level (no education or unfinished, primary or secondary education, and higher education or college), workplace environment (proper air-conditioned, poorly air-conditioned, outdoor work, unemployed), social and family circumstances (living as part of a family or in a partnership, single, living in an institution or residence, or living in shared housing), home environment (well air-conditioned, airy).

Use of diagnostic tools. We recorded the use of anterior rhinoscopy or nasal endoscopy (to assess oedema, congestion, or mucopurulent secretion from the middle meatus), imaging techniques (X-ray, CT scan), and microbiological cultures (culture of nasal secretions). This information was recorded at Visits 1 and 2 in order to know the tests performed before (by PCPs) and after (by ORLs) the inclusion in the study.

Prescription of medications. Prescribed medications, either recommended (antibiotics, intranasal corticosteroids, nasal saline irrigation, nasal decongestants, phytotherapy) or non-recommended (antibiotics, antihistamines, mucolytics) by EPOS consensus to treat ARS, were recorded at Visits 1 and 2.

Episode duration and disease severity. Duration of symptoms (days) was recorded at Visits 1 and 2, as at Visit 3 when needed. Severity was assessed at Visits 1 and 2 by using a visual analogue scale (VAS, 0-10cm)[1] after answering the question *"how troublesome are your symptoms of rhinosinusitis?"* (0, not troublesome, to 10, worst imaginable). Disease severity was assessed by using a visual analogue scale (VAS, 0-10cm) and classified as mild (VAS 0-3cm), moderate (VAS >3-7cm), or severe (VAS >7-10cm).[1, 26]

Quality of Life and health status. Sino-nasal Outcome Test (SNOT)-16 questionnaire was used to assess the impact of disease and its treatment on quality of life at both Visits 1 and 2. Each of the 16 items was scored from 0 (not affected) to 5 (extremely affected). The overall score runs from 0 (better QoL) to 80 (worst QoL). The general health status prior to and during the disease was recorded using a visual analogical scale (0-10cm).

Disease complications. Instead of recording the presence of complications, the study recorded the presence of symptoms linked to complications, as stated by EPOS guidelines.[25] Orbital symptoms (palpebral oedema, orbital pain, diplopia, exophthalmos, decrease in visual acuity), neurological symptoms (meningeal symptoms, neurological deficit), and frontal symptoms (frontal oedema, severe frontal pain) were assessed. In addition, other sinonasal signs and symptoms of a potential different disease involved were also recorded (unilateral symptoms, bleeding, crusts, lacrimation and conjunctiva hyperemia, or cacosmia).

Data management & statistical analysis

Study size. This was an observational study, without a specific hypothesis as the main objective. Therefore, the sample size was determined by logistical and cost reasons rather than by analytical criteria.

Sociodemographic characteristics, nasal symptoms, use of diagnostic tools, prescribed medications, disease severity, and quality of life were compared between patients with viral (common cold) and postviral RSA. Differences in quantitative measures were evaluated by Student's t test for independent groups and differences in qualitative measures were assessed with the Chi-square or Fisher's exact test as appropriate. The improvement in patient's quality of life (SNOT-16) between Visits 1 and 2 was evaluated by Student's t test for paired groups.

Logistic regression models were estimated to assess the associations with postviral RSA using viral RSA as the reference group. The relationship between treatments (medication) and disease duration, quality of life at Visit 2 and the risk of complications were also assessed. These associations were evaluated by linear regression using the duration and the total score of SNOT-16 in logarithmic scale, and by logistic regression for the complications assessment. Multivariate regression models were estimated by a backward selection procedure using 0.05 as significance level for removal from the model. All regression models were adjusted for the study group (viral and postviral ARS).

Additionally, regression models to evaluate associations between medication and duration, or medication and complications, were also adjusted for severity at recruitment, whereas models to evaluate associations between medication and quality of life at Visit 2 were adjusted for quality of life at visit 1. Interactions between treatments were also assessed. Statistical analysis was performed using Stata version 14 (Stata Corp., Texas, USA).

RESULTS

Demographic characteristics

From the initial 1,678 patients included at Visit 1, 1,499 (89%) completed Visit 2, with 1,362 patients being considered valid for the study **(Figure 1**). Patients were classified into three groups according to the duration of symptoms of rhinosinusitis: 36% (n=494) had viral ARS (common cold) with a mean duration of 6.0 days (95%CI: 5.9-6.2), 63% (n=857) had postviral ARS with a mean duration of 16.5 days (95%CI: 15.8-17.3), and 1% (n=11) had chronic symptoms (CRS). Patients with CRS were excluded from this analysis and therefore the sample size for analysis was 1,351 patients (36% with viral and 63% with postviral ARS). By definition, all patients with viral ARS were cured before 10 days. From those with postviral ARS, 74.3% of episodes were resolved before Visit 2, and 25.7% in the time between Visits 2 and 3 **(Figure 1**).

More women (53%) than men participated in the study, with a similar ratio appling to both viral and postviral ARS sample groups. Both groups were also homogenous concerning weight, height, or ethnicity. Most patients (81%) lived in an urban environment, with no differences between disease groups (**Table 1**). Concerning workplace, most patients with either viral (68%) or postviral (63%) ARS worked in a well air-conditioned environment. Patients working in a poorly air-conditioned environment were significantly higher in postviral (13%) than viral (8%) ARS, p=0.0092. Half of patients (46%) reported a previous history of ARS episodes without differences between groups.

Nasal symptoms

Nasal congestion/obstruction/blockage (98%) and anterior/posterior nasal discharge (95%) were the most frequent symptoms of ARS, followed by facial pressure/pain (77%) and reduction/loss of smell (60%). No differences were found between patients with viral and postviral ARS (**Table 2**). By excluding nasal discharge in the postviral ARS group, the frequency of symptoms were however significantly higher ($p<0.05$) when disease severity increased, and this was more relevant for hyposmia and facial pressure/pain in postviral ARS **(Figure 2).**

Disease severity

Severity by VAS for postviral ARS was slightly higher (7.13±1.48cm) than for viral ARS (6.98±1.60cm), although this was not statistically significant**.** The general health status (VAS) during the disease episode was also similar in viral (5.45±1.89cm) and in postviral ARS (5.59±1.89cm), but significantly affected when compared to the general health status they had retrospectively, before the episode (8.85±1.40cm and 8.67±1.76cm, respectively).

When comparing viral and postviral ARS, all three levels of severity were similar (mild: 2.65±0.57cm vs 2.72±0.57cm; moderate: 6.11±0.97cm vs 6.09±1.00cm; and severe: 8.36±0.60 vs 8.35±0.64). In addition, no differences were found between viral and postviral ARS in general health status (VAS) in the three severity levels, either before (retrospective) or during the disease.

Quality of life (SNOT-16)

At Visit 1, SNOT-16 global score was worse in postviral (38.7±14.2, p=0.0031) than in viral RSA (36.0±15.3). In addition, a higher SNOT-16 score was strongly related to a higher disease severity degree in both viral and postviral ARS (p<0.0001)**.** At Visit 2, SNOT-16 global score significantly improved compared to Visit 1 for both postviral (15.9±15.9, p<0.0001) and viral ARS (14.1±17.2, p<0.0001). No significant differences (p=0.0726) between viral and postviral groups were found for the SNOT-16 score (**Figure 3).**

Diagnostic tools

Overall, including all tests conducted before and after patients were recruited for the study, the diagnostic tools most frequently performed were anterior rhinoscopy/nasal endoscopy (76%), X-ray (64%), CT scan (18%), and microbiology cultures (7%)**,** with all of them being more frequent (p<0.0002) in postviral than in viral ARS (**Figure 4**). PCPs performed more X-ray (45% vs. 36%, p<0.0001) than ORLs, who performed more rhinoscopy/endoscopy (68% vs. 27%, p<0.0001), CT scans (15% vs. 5%, p<0.0001), and microbiology cultures (5% vs. 2%, p<0.0001). Concerning disease severity, the performance of X-ray increased with higher levels of severity in postviral (p=0.0045) but not in viral (p=0.0606) ARS. In contrast, the performance of CT-scan increased with higher severity levels in viral (p=0.0024) but not in postviral ARS (p=0.2631).

Medications

In viral and postviral ARS, the most frequently prescribed medication was, respectively, oral antibiotic (62% vs. 76%), topical steroids (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%). All drugs were more frequently prescribed in postviral than in viral ARS patients ($p<0.0006$ for all comparisons), except for nasal phytotherapy ($p= 0.1413$) **(Figure 5).**

There were only a few patients (3%) who did not receive any treatment, while most of ARS patients received more than one medication. Based on EPOS recommendations, oral antibiotics were incorrectly prescribed in 62% of viral ARS (common cold), while only 54% of postviral ARS patients were treated with intranasal corticosteroids **(Table 3).**

In addition, PCPs prescribed more oral antibiotics (53% vs. 39%, $p<0.0001$), antihistamines (26% vs. 22%, $p=0.0068$), nasal decongestants (34% vs. 18%, $p<0.0001$), mucolytics (45% vs 21%, $p<0.0001$), and intranasal saline (34% vs. 25%, $p<0.0001$) than ORLs. However, ORLs prescribed more nasal phytotherapy (39% vs. 9%, $p<0.0001$) and showed a tendency to prescribe more intranasal corticosteroids (30% vs. 26%, $p=0.0721$) than PCPs **(Figure 5).**

Concerning disease severity, antibiotics and mucolytics were more frequently prescribed in severe cases of both viral and postviral ARS ($p<0.0225$ for all comparisons), while antihistamines were more prescribed in severe viral ARS ($p=0.0040$), and nasal decongestants ($p=0.0408$) in severe postviral ARS.

No significant association was found between medication and quality of life

(SNOT-16 score) or the risk of complications at visit 2. Interactions between treatments were also assessed, although none of them showed a statistically significant difference.

Disease complications

More patients with postviral (1.5%) than viral ARS (0.4%) had signs or reported symptoms potentially linked to rhinosinusitis complications, such us ophthalmic, neurological, or frontal (p=0.0603). In addition, there were patients who reported other unusual signs and symptoms (5.6% in postviral and 3% in viral ARS) that could potentially be linked to a different diagnosis **(Table 4).** No differences were found when comparing disease severity degrees.

Factors associated with disease duration

All population characteristics were analysed to identify factors associated with postviral ARS development. **Table 5** shows the crude estimates for Odds Ratios using viral ARS as a reference group. In the multivariate analysis we found that working in a poorly air-conditioned enclosure was the only factor significantly associated with developing postviral ARS (OR: 2.26; 95%CI: 1.27-4.04).

The analysis of associations between medication and duration, adjusted for type of RSA (viral / postviral) and severity at baseline, showed a longer duration of the episode in patients who took nasal decongestants, saline solutions, antibiotics or intranasal corticosteroids than in those who did not. According to multivariate analysis, phytotherapy (mainly *Cyclamen europaeum, CE*) was related with shorter duration (Odds Ratio: 0.95 [0.91-1.00], p=0.0480), although

intranasal corticosteroids were related with longer duration (Odds Ratio: 1.07 [1.02-1.12], p=0.0048).

DISCUSSION

The most significant findings of the PROSINUS study were: 1st) ARS was mostly a self-limited disease, with only 1% of chronification; 2nd) working in a poorly air-conditioned environment was a risk factor for common cold to develop into postviral ARS; 3rd) both PCPs and ORLs performed a high number of non-indicated diagnostic tools, mainly plane X-Ray; 4th) ORLs and especially PCPs prescribed a large number of non-recommended medications, with antibiotics being the most significant, followed by mucolytics and antihistamines; 5th) intranasal corticosteroids were less frequently prescribed by ORLs and even less so by PCPs; and 6th) there was an association between prescribed intranasal corticosteroids and a longer duration of ARS, and prescribed phytotherapy (*CE)* and shorter disease episodes.

In the present study only 1% of chronification was found, suggesting that most ARS cases tend to be cured independently of the prescribed treatment. Spontaneous cure with no treatment has been identified in 80% of ARS patients[27]. Working in a poorly air-conditioned environment was the only identified risk factor (OR: 2.26) in developing postviral ARS. Previous studies have suggested the importance of other factors such as contact with people with upper respiratory complaints[28], winter months (January to March) having a risk factor (OR: 2.9) to develop ARS compared to July to September[29], allergic rhinitis developing in postviral ARS (OR: 4.4) compared to healthy controls[30], and active[31] and passive[32] smoking. In our study the most prevalent symptoms, in both common cold and postviral ARS, were nasal congestion (98%) and discharge (95%), followed by facial pressure/pain (77%) and smell

loss (60%). Although the presence of nasal symptoms was biased by inclusion criteria, facial pressure/pain and smell loss were highly associated with severe ARS. In a French study done by PCPs, similar findings were reported in patients with Acute Maxillary Sinusitis.[2] Despite the EPOS guidelines[1] stating that the diagnosis of ARS is mainly clinical (based on symptoms) and supported by nasal examination (anterior rhinoscopy or nasal endoscopy), in our study, many ORLs and particularly PCPs did not perform nasal examination (68% and 27% respectively) in ARS patients. Plain X-ray has proven to have poor sensitivity and specificity[33,34] and is not recommended in the diagnosis of ARS[35]. Since Gwaltney et al.[36] reported that CT scans show sinus opacity in most patients (87%) with common cold, this imaging technique is only recommended in complicated cases [11]. The present study shows however that physicians from Spain performed a high number of plain X-ray and CT scan in postviral ARS (70% and 22%, respectively) but also in common cold (55% and 12%, respectively), with plain X-ray predominantly being carried out by PCPs, and CT scan by ORLs. These practices were not related to suspected complications since the frequency of symptoms suggesting complications were very low (0.4% in common cold and 1.5% in postviral ARS).

Although VAS has been validated to assess CRS severity[1, 25, 26], our study has been the first to use it to assess ARS severity. Interestingly, VAS score was similar in both viral and postviral ARS suggesting that disease severity is not associated with the duration of disease. Patients with severe ARS have more smell loss, more facial pain, and more impact on quality of life than patients with moderate and mild ARS. Moreover, plane X-Ray was more often indicated, and

antibiotics more generally prescribed in patients with severe ARS. On the other hand, the presence of symptoms linked to complications was not different between severity groups. Previous studies have reported the impact of ARS on quality of life and its improvement with intranasal corticosteroids[37] or antibiotics[14] using SNOT-20 and SNOT-16, respectively. In our study, postviral ARS had a higher impact on quality of life than common cold but, in both groups, QoL improved and reached normal values no matter the treatment used for 2-4 weeks.

Although guidelines suggest that a diagnosis of bacterial ARS should be considered in patients with fever, severe unilateral pain, purulent rhinorrea, and double sickening[38], there are real difficulties to differentiate between postviral and bacterial ARS. Several studies have reported an overuse of antibiotic prescriptions by PCPs. Dutch PCPs prescribed antibiotics in 34% of patients with moderate ARS[39] while US PCPs did so in 82.3% of ARS cases[40]. In addition, ARS was behind 3.9% of all diagnoses with antibiotic prescription performed by PCPs[41]. In our study, Spanish physicians prescribed antibiotics in most of the ARS cases either in common cold (62%) or in postviral ARS (76%). However, not only PCPs but also ORLs overused the antibiotic prescription (53% and 39% respectively). A potential explanation for this could be that PCPs may consider the term “sinusitis” as synonym of bacterial ARS instead of being considered as an inflammatory condition. [42]

Current guidelines[1,37] and recent systematic reviews[20, 43] recommend the use of oral antibiotics in combination with intranasal corticosteroids only in severe

bacterial ARS or in complications. Yet, there are no indications for cases of mild to moderate non-complicated ARS. The potential benefit of antibiotics in treating ARS should be contrasted with the potential of inducing antibiotic resistance and the very low incidence of serious complications.[19,20] Many recent studies have addressed the high costs of antibiotic resistance.[41] Kraker et al.[44] calculated the cost related to *Staphyloccocus aureus* and *Escherichia coli* infections and their antibiotic resistance in Europe resulting in 8,000 deaths and 62 million Euros for 2007. Surprisingly, the incidence of infections by resistant bacteria was higher in countries with high use (i.e. Portugal) compared to those with lower use (i.e. Iceland or Norway) of antibiotics. Similarly, Carter et al.[45] calculated the cost of infections produced by pan-drug-resistant gram negative bacteria in the UK in an estimated 79,000 deaths over a 20-year period. Concerning the role of antibiotics on preventing complications, Babar-Craig et al.[46] reported that complications requiring surgical intervention were similar in patients receiving antibiotic treatment or not. In the Netherlands, Hansen et al.[10] reported a very low rate of ARS complications in both children (1:12,000) and adult (1:32,000) patients which suggested antibiotic treatment did not prevent complications. In our study, the frequency of symptoms suggesting complications was totally independent of the prescribed medication.

Although the efficacy of intranasal corticosteroids in ARS remains controversial, current guidelines[1] and systematic reviews [18,47] recommend the use of intranasal corticosteroids (INS) in moderate (monotherapy) and severe (in combination with antibiotics) ARS. Dolor et al.[17] firstly described that the addition of INS (fluticasone propionate) to antibiotic treatment improved clinical

success rates and accelerated recovery. Further studies demonstrated the superiority of INS (mometasone furoate) in monotherapy over placebo and even over amoxicillin to improve nasal symptoms[48,49] and QoL[37] in patients with moderate non-complicated ARS. However these benefits are only clear when INS are used in high doses and during almost three weeks[18,48]. In common cold however INS are not related to better cure rates or symptom relieve[50]. In our study, Spanish physicians prescribe INS in two out of five (38%) patients with common cold and in one out of two (54%) patients with postviral ARS, with INS prescription being associated with a longer duration of the disease. As long as the present study is a real life study, a cause-effect relationship cannot be stated (see the limitations of the study at the end of this section), since physicians may reserve INS treatment for cases with more prolonged disease. Some studies have described the efficacy of herbal medicines such as Myrtol,[51] Pelargonium sidoides,[52], and recently BNO 1016[53]. In 2012, Pfaar et al.,[54] reported that CE added-on to antibiotics reached a better symptom control of ARS compared to placebo. In consequence, EPOS guidelines recommended their use in adult ARS[1]. A recent meta-analysis by Kock et al.[24] has confirmed the efficacy of some herbal compounds such as EPs 7630, myrtol, BNO 101, BNO 1016, *Cyclamen europaeum (CE),* and Esberitox. In the present study, an association was found between the use of *CE* and a shorter disease duration suggesting *CE* be accepted by physicians as a treatment choice for ARS. In 2011 Wang et al.[27] published a study reporting a huge amount of medications prescribed in Asia to treat mild ARS (common cold). Over 80% of GPs and ENTs prescribed at least one medication in ARS, with antihistamines (39.2%) and nasal decongestants (33.6%) being among the

medications most frequently prescribed. Despite the fact that antihistamines and mucolytics have not shown any benefit on treating ARS, and are not recommended by international guidelines[1], physicians, and especially PCPs but also ENT specialists, in our study regularly prescribed antihistamines (26%) and mucolytics (45%) to ARS patients.

In summary, the management of mild to moderate ARS is quite similar as for severe/bacterial ARS (apart from the need of antibiotics in specific cases) as disease can be expected to resolve even when moderate or severe symptoms are present. The use of intranasal corticosteroids appears to help benefit the resolution of disease.

Weaknesses and Strengths

As with all epidemiological studies, the PROSINUS survey may have some weaknesses and limitations. 1) The study population cannot be considered a random sample since there was no control over which patients received specific medications, or in which patients diagnostic tools were performed. We have attempted to address this by estimating regression models adjusted for the RSA type and severity level at Visit 1. In addition, the results have been interpreted in terms of association, avoiding any interpretation in terms of causality. 2) The management performed by PCPs (retrospective) and ORLs (prospective) cannot directly be compared since they were not parallel but consecutive groups, with the same patients but assessed at different times. In addition, some unmet needs were identified in the study: clear validated criteria to define bacterial ARS, physicians' criteria to prescribing antibiotics.

On the other hand our strengths are: 1) the high number of included patients,

and that EPOS criteria were followed for inclusion criteria and to classify our patient's population; and 2) the study is a real life and prospective providing a real approach of physician behaviour in their daily clinical practice concerning the management of disease.

Although this study is based in data collected in 2007, ARS has not suffered significant changes in either available diagnostic tools or therapeutic options since then in Spain. In addition, overuse of antibiotics remain a significant burden for many diseases in our society. In consequence, we consider these findings as very relevant for the current clinical practice.

CONCLUSIONS

To summarize our findings, we can conclude that despite the fact that consensus guidelines on ARS management have existed for more than a decade, a lot of diagnostic tools are still performed unnecessarily, and a lot of non-recommended medications are prescribed to treat a disease that is mostly self-limited. There is an important unmet need to educate physicians as much as policymakers to manage ARS following evidence-based clinical practice guideline recommendations. It has been proved that the education is effective to reduce antibiotic prescriptions for respiratory tract infections[55] and ARS[56]. We found an overuse of diagnostic tools and prescribed medications but, in addition to the burden and mortality induced by antibiotic resistance due to antibiotic overuse, the associated direct and indirect costs remain to be analysed.

ACKNOWLEDGEMENTS

To all centres and specialists in otolaryngology from Spain who participated in the PROSINUS study.

DATA SHARING STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; JM is or has been member of national and international scientific advisory boards (consulting), received fees for lectures, and grants for research projects from ALK-Abelló, FAES, Genentech-Roche, GSK, Hartington Pharmaceuticals, MEDA Pharma, Menarini, MSD, Novartis, Sanofi-Genzyme-Regeneron, UCB, and Uriach Group. No other relationships or activities that could appear to have influenced the submitted work.

The manuscript is an honest, accurate, and transparent account of the study being reported, and no important aspects of the study have been omitted.

FUNDING

The PROSINUS study was partially sponsored by an unrestricted research grant from Hartington Pharmaceuticals.

CONTRIBUTORS

FJ is the guarantor of the study, and has contributed with the conception and design of the study, literature search, acquisition of data, analysis and interpretation of data and writing the manuscript.

LQ has contributed with the study design, acquisition of data, statistical analysis and interpretation of data and drafting the manuscript and approving its final version.

IA has contributed through literature research, interpretation of data and by drafting the manuscript and approving its final version.

JM has contributed with the conception and design of the study, acquisition of data, analysis and interpretation of data and a critical reading of the manuscript and approving its final version.

FIGURE LEGENDS

Figure 1. Flow-chart of participants in the PROSINUS study. Two phenotypes for acute (ARS) and one for chronic (CRS) rhinosinusitis were analysed: patients with viral ARS / common cold (36%), postviral ARS (63%), and chronic rhinosinusitis (1%). VAS, Visual Analogue Scale. Concerning percentages: (a) % refers to patients selected at Visit 1 (N=1,678); (b) % refers to patients considered valid at Visit 2 (N=1,362).

Figure 2. Frequency of symptoms in acute rhinosinusitis patients. Bars represent the frequency (%) of individual sinonasal symptoms in each level of severity for both viral and postviral acute rhinosinusitis (ARS). Reported frequency of symptoms was always higher in the highest severity level. *, $p<0.05$; NS, not significant.

Figure 3. Quality of life (SNOT-16) in acute rhinosinusitis patients. Changes in the individual values (solid lines) and in the average values of each group (dashed lines). At baseline, SNOT-16 score was more affected (*, $p<0.05$) in postviral than in viral acute rhinosinusitis (ARS). SNOT-16 score significantly improved (‡, $p<0.05$) after disease resolution with no differences between both ARS phenotypes.

Figure 4. Diagnostic tools performed in acute rhinosinusitis patients. Percentage of patients undergoing different diagnostic tools, for both viral and

postviral acute rhinosinusitis, recommended by either Primary Care Physicians or Otorhinolaryngologists. *, p<0.05; NS, not significant.

Figure 5. Prescribed medications in acute rhinosinusitis patients. Percentage of patients being treated with different medications, for both viral and postviral acute rhinosinusitis (ARS), prescribed by either Primary Care Physicians or Otorhinolaryngologists. *, p<0.05; NS, not significant.

Table 1. Socio-demographic characteristics of acute rhinosinusitis (ARS) study population

Demographic characteristics		Viral ARS (N=494)	Postviral ARS (N=857)	Total ARS (N=1,351)	p-value
Age [1]		42.2 ±14.3 (424)	42.6±14.0 (761)	42.4±14.1 (1185)	0.6871 [2]
Gender [3]	Men	234/471 (50)	375/821 (46)	609/1,292 (47)	0.1651 [4]
Area of residence [3]	Rural	23 (5)	52 (6)	75 (6)	0.1094 [4]
	Semi-rural	52 (11)	120 (15)	172 (13)	
	Urban	392 (84)	653 (79)	1,045 (81)	
	Total	467 (100)	825 (100)	1,292 (100)	
Place of residence [3]	With family / couple	440 (89)	748 (88)	1,188 (88)	0.4976 [5]
	Single	44 (9)	91 (11)	135 (10)	
	Institution / residence	4 (1)	3 (0)	7 (1)	
	Shared housing	6 (1)	11 (1)	17 (1)	
	Total	494 (100)	853 (100)	1,347 (100)	
Education level [3]	No / unfinished education	45 (9)	84 (10)	129 (10)	0.2855 [4]
	Primary / secondary education	219 (45)	415 (49)	634 (47)	
	College / higher education	225 (46)	355 (42)	580 (43)	
	Total	489 (100)	854 (100)	1,343 (100)	
Daily activity [3]	Well air-conditioned enclosure	332 (68)	534 (63)	866 (65)	0.0092 [4]
	Poorly air-conditioned enclosure	37 (8)	113 (13)	150 (11)	
	Outdoors	38 (8)	54 (6)	92 (7)	
	Unemployed	78 (16)	146 (17)	224 (17)	
	Total	485 (100)	847 (100)	1,332(100)	
Well air-conditioned home [3]		449/477 (94)	751/823 (91)	1,200/1,300 (92)	0.0605 [4]
Airy home [3]		395/415 (95)	731/757 (97)	1,126/1,172 (96)	0.2430 [4]

1, Arithmetic mean±SD (n)
2, Student t-test
3, n (%)
4, Chi-squared test
5, Fisher's exact test

Table 2. Frequency of symptoms in viral/postviral acute rhinosinusitis (ARS)

	Viral ARS (N=494)	Postviral ARS (N=857)	p-value
Nasal obstruction [1]	481/493 (98)	829/857 (97)	0.3847[2]
Rhinorrea [1]	464/490 (95)	800/854 (94)	0.4482[2]
Facial pressure/pain [1]	370/485 (76)	653/848 (77)	0.7659[2]
Loss of smell [1]	275/470 (59)	533/847 (63)	0.1148[2]

1, number of cases and proportion within group (%)
2, Chi-squared test

Table 3. Frecuency of recommended combined medications in acute rhinosinusitis (ARS).

Recommended medications		Viral ARS (N=494)	Postviral ARS (N=857)	Total ARS (N=1,351)	p-value
No treatment [1]		27 (5)	20 (2)	47 (3)	0.0025 [2]
Antibiotic [1]	AB (total)	308 (62)	648 (76)	956 (71)	< 0.0001 [2]
	AB alone	13 (3)	6 (1)	19 (1)	0.0037 [2]
	AB in combination (except with CS)	137 (28)	261 (30)	398 (29)	0.2905 [2]
Intranasal CS [1]	Topical CS (total)	188 (38)	463 (54)	651 (48)	< 0.0001 [2]
	Topical CS alone	1 (0)	1 (0)	2 (0)	1.0000 [3]
	Topical CS in combination (except with Ab)	29 (6)	81 (9)	110 (8)	0.0204 [2]
Phytoteraphy [1]	Phytoteraphy (total)	205 (41)	391 (46)	596 (44)	0.1413 [2]
	Phytoteraphy alone	20 (4)	9 (1)	29 (2)	0.0002 [2]
	Phytoteraphy in combination (except with AB or CS)	39 (8)	46 (5)	85 (6)	0.0654 [2]
Antibiotic + intranasal CS [1]	AB + topical steroids alone	12 (2)	4 (0)	16 (1)	0.0013 [2]
	AB + topical CS in combination	146 (30)	377 (44)	523 (39)	< 0.0001 [2]
Saline solutions [1]	Saline solutions (total)	197 (40)	462 (54)	659 (49)	< 0.0001 [2]
	Saline solutions alone	9 (2)	4 (0)	13 (1)	0.0193 [3]
	Saline solutions in combination	188 (38)	458 (53)	646 (48)	< 0.0001 [2]
Other combinations without AB, intranasal CS or phytotherapy [1]		70 (14)	52 (6)	122 (9)	< 0.0001 [2]
Mucolitics [1]		235 (48)	515 (60)	750 (56)	< 0.0001 [2]
Antihistamines [1]		154 (31)	396 (46)	550 (41)	< 0.0001 [2]
Nasal decongestants [1]		190 (38)	412 (48)	602 (45)	0.0006 [2]

1 number of cases and proportion within group (%)
2 Chi-squared test
3 Fisher's exact test
AB, antibiotic; ARS, acute rhinosinusitis; CS, corticosteroids.

Table 4. Frequency of unusual symptoms and symptoms suggesting a complication of acute rhinosinusitis (ARS).

			Total ARS (N=1,351)	Viral ARS (N=494)	Postviral ARS (N=857)	p-value
Unusual symptoms (consider different diagnosis) [1]	Total		49 (3.6)	12 (2.4)	37 (4.3)	0.0738 [2]
	Unilateral symptoms		8 (0.6)	2 (0.4)	6 (0.7)	0.7179
	Bleeding		30 (2.2)	8 (1.6)	22 (2.6)	0.2549
	Crusts		10 (0.7)	2 (0.4)	8 (0.9)	0.3419
	Lacrimation and conjunctiva hyperaemia		13 (1)	3 (0.6)	10 (1.2)	0.3950
	Cacosmia		2 (0.1)	0 (0)	2 (0.2)	0.5358
Symptoms suggesting a complication [1]	Total		15 (1.1)	2 (0.4)	13 (1.5)	0.0603 [2]
	Orbital symptoms	Total	9 (0.7)	1 (0.2)	8 (0.9)	0.1673 [3]
		Palpebral oedema	6 (0.4)	1 (0.2)	5 (0.6)	0.4246
		Exophthalmos	0 (0)	0 (0)	0 (0)	_
		Diplopia	1 (0.1)	0 (0)	1 (0.1)	1.0000
		Ocular pain	5 (0.4)	0 (0)	5 (0.6)	0.1652
		Decrease of visual acuity	2 (0.1)	0 (0)	2 (0.2)	0.5358
		Other orbital symptoms	2 (0.1)	0 (0)	2 (0.2)	0.5358
	Frontal symptoms	Total	9 (1.1)	1 (0.2)	8 (0.9)	0.1673 [3]
		Intense frontal pain	9 (0.7)	1 (0.2)	8 (0.9)	0.1673
		Frontal oedema	1 (0.1)	0 (0)	1 (0.1)	1.0000
	Neurologic symptoms		0 (0)	0 (0)	0 (0)	_
	Systemic symptoms		0 (0)	0 (0)	0 (0)	_

1 number of cases and proportion within group (%)
2 Chi-squared test
3 Fisher's exact test

Table 5. Risk factors for a viral leading to a postviral acute rhinosinusitis (ARS).

		Viral ARS (N=237)	Postviral ARS (N=452)	Total ARS (N=689)	OR	95% CI	p
Age [1]		42.3±14.3 (237)	42.2±13.7 (452)	42.3±13.9 (689)	1.00	(0.99; 1.01)	0.9104
Gender [2]	Men	111 (47)	208 (46)	319 (46)	1		0.8380
	Women	126 (53)	244 (54)	370 (54)	1.03	(0.75; 1.42)	
	Total	237 (100)	452 (100)	689 (100)			
Area of residence [2]	Rural	12 (5)	20 (4)	32 (5)	1		0.5672
	Semi-rural	26 (11)	62 (14)	88 (13)	1.43	(0.61; 3.35)	
	Urban	199 (84)	370 (82)	569 (83)	1.12	(0.53; 2.33)	
	Total	237 (100)	452 (100)	689 (100)			
Place of residence [2]	With family / couple	210 (89)	399 (88)	609 (88)	1		
	Alone	23 (10)	48 (11)	71 (10)	1.10	(0.65; 1.86)	0.9064
	Institution / residence	1 (0)	1 (0)	2 (0)	0.53	(0.03; 8.46)	
	Shared housing	3 (1)	4 (1%)	7 (1%)	0.70	(0.16; 3.16)	
	Total	237 (100)	452 (100)	689 (100)			
Education level [2]	No / unfinished education	13 (5)	30 (7)	43 (6)	1		0.4829
	Primary / secondary education	106 (4)	218 (48)	324 (47)	0.89	(0.45; 1.78)	
	College / higher education	118 (50)	204 (45)	322 (47)	0.75	(0.38; 1.49)	
	Total	237 (100)	452 (100)	689 (100)			
Daily activity [2]	Well air-conditioned enclosure	171 (72)	302 (67)	473 (69%)	1		0.0323
	Bad air-conditioned enclosure	16 (7)	64 (14)	80 (12)	2.26	(1.27; 4.04)	
	Outdoors	17 (7)	23 (5)	40 (6)	0.77	(0.40; 1.47)	
	Unamployed	33 (14)	63 (14)	96 (14)	1.08	(0.68; 1.71)	
	Total	237 (100)	452 (100)	689 (100)			
Well heated home [2]		221 / 237 (93)	407 / 452 (90)	628 / 689 (91)	0.65	(0.36; 1.19)	0.1620
Airy home [2]		229 / 237 (97)	440 / 452 (97)	669 / 689 (97)	1.28	(0.52; 3.18)	0.5933

1 Arithmetic Mean ± SD (n)
2 number of cases and proportion within group (%)

BIBLIOGRAPHY

1. Fokkens WJ, Lund VJ, Mullol J, et al. The European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinology* 2012;50(Suppl 23):1-299

2. Klossek J, Mesbah K. Presentation and treatment of acute maxillary sinusitis in general practice: A French observational study. *Rhinology* 2011;49-1:84-9.

3. Stjärne P, Odebäck P, Ställberg B, et al. High costs and burden of illness in acute rhinosinusitis: real-life treatment patterns and outcomes in Swedish primary care. *Prim Care Respir J* 2012;21:174-9

4. Passioti M, Maggina P, Megremis S, et al. The common cold: potential for future prevention or cure. *Curr Allergy Asthma Rep* 2014;14:413.

5. Van Kempen M. An update on the pathophysiology of rhinovirus upper respiratory tract infections. *Rhinology*1999;37:97-103.

6. Berg O, Carenfelt C, Rystedt G, Anggard A. Occurrence of asymptomatic sinusitis in common cold and other acute ENT-infections. *Rhinology* 1986;24:223-5.

7. Smith SS, Ference EH, Evans CT, et al. The prevalence of bacterial infection in acute rhinosinusitis: a Systematic review and meta-analysis. *Laryngoscope 2015*;125:57-69.

8. Turner RB. Epidemiology, pathogenesis and treatment of the common cold. *Ann Allergy Asthma Immunol* 1997;78:531-40.

9. Oskarsson JP, Halldorsson S. Anevaluation of diagnosis and treatment of acute sinusitis at three healthcare centers. *Laeknabladid* 2010;96:531-5.

10. Hansen FS, Hoffmans R, Georgalas C, et al. Complications of acute rhinosinusitis in The Netherlands. *Fam Pract* 2012;29:147-53.

11. Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in Rhinology EAACI position paper. *Clin Transl Allergy* 2011;1:2.

12. Ebell MH, McKay B, Guilbault R, et al. Diagnosis of acute rhinosinusitis in primary care: a systematic review of test accuracy. *Br J Gen Pract* 2016;66:e612-32.

13. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev* 2008;16:CD000243.

14. Garbutt JM, Banister C, Spitznagel E, et al. Amoxicillin for acute rhinosinusitis: a randomized controlled trial. *JAMA* 2012;307:685-92.

15. Ahovuo-Saloranta A, Rautakorpi UM, Borisenko OV, et al. Antibiotics for acute maxillary sinusitis in adults. *Cochrane Database Syst Rev* 2014;11:CD000243.

16. Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.

17. Dolor RJ, Witsell DL, Hellkamp AS, et al. Ceftin and Flonase for Sinusitis (CAFFS) Investigators. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. *JAMA* 2001;286:3097-105.

18. Hayward G, Heneghan C, Perera R, et al. Intranasal corticosteroids in management of acute sinusitis: a systematic review and meta-analysis. *Ann Fam Med* 2012;10:241-9.

19. Smith SR, Montgomery LG, Williams JW Jr. Treatment of mild to moderate sinusitis. *Arch Intern Med* 2012;172:510-3.

20. Lemiengre MB, van Driel ML, Merenstein D, et al. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. *Cochrane Database Syst Rev* 2012;10:CD006089.

21. Passali GC, et al. A prospective open-label study to assess the efficacy and safety of a herbal medicinal product (Sinupret) in patients with acute rhinosinusitis. *ORL J Otorhinolaryngol Relat Spec* 2015;77:27-32.

22. Mullol J, Crespo C, Carré C, Brosa M. *Pharmacoeconomics of Cyclamen europaeum* in the management of acute rhinosinusitis. *Laryngoscope* 2013;123:2620-5.

23. Ponikau JU, Hamilos DL, Barreto A, et al. An exploratory trial of *Cyclamen europaeum* extract for acute rhinosinusitis. *Laryngoscope* 2012;122(9):1887-92.

24. Koch AK, Klose P, Lauche R, et al. A Systematic Review of Phytotherapy for Acute Rhinosinusitis. *Forsch Komplementmed* 2016;23:165-9.

25. Fokkens W, Lund V, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2007. European Position Paper on Rhinosinusitis and Nasal Polyps group. *Rhinology* 2007;Suppl 20:1-136.

26. Lim M, Lew-Gor S, Darby Y, et al. The relationship between subjective assessment instruments in chronic rhinosinusitis. *Rhinology* 2007;45:144-7

27. Wang DY, Wardani RS, Singh K, et al. A survey on the management of acute rhinosinusitis among Asian physicians. *Rhinology* 2011;49:264-71.

28. Van Gageldonk-Lafeber AB, van der Sande MA, Heijnen ML, et al. Risk factors for acute respiratory tract infections in general practitioner patients in The Netherlands: a case-control study. *BMC Infect Dis* 2007;7:35.

29. Van Gageldonk-Lafeber AB, Heijnen ML, Bartelds AI, et al. A case-control study of acute respiratory tract infection in general practice patients in The Netherlands. *Clin Infect Dis* 2005;4:490-7.

30. Schatz M, Zeiger RS, Chen W, et al. The burden of rhinitis in a managed care organization. *Ann Allergy Asthma Immunol* 2008;101:240-7.

31. Zuskin E, Mustajbegovic J, Schachter EN, et al. Respiratory findings in mail carriers. *Int Arch Occup Environ Health* 2000;73:136-43.

32. Bonham GS, Wilson RW. Children's health in families with cigarette smokers. *Am J Public Health* 1981;71:290-3.

33. Jonas I, Mann W. Misleading x-ray diagnosis due to maxillary sinus asymmetries (author's transl). *Laryngol Rhinol Otol (Stuttg)* 1976;55:905-13.

34. McAlister WH, Lusk R, Muntz HR.Comparison of plain radiographs and coronal CT scans in infants and children with recurrent sinusitis. *AJR Am J Roentgen*ol 1989;153:1259-64.

35. Bird J, Biggs TC, Thomas M, Salib RJ. Adult acute rhinosinusitis. *BMJ* 2013;346:f2687.

36. Gwaltney JM, Phillis CD, Miller RD, et al. Computed tomographic study of the common cold. *N Eng J Med* 1994;330:25-30.

37. Bachert C, Meltzer EO. Effect of mometasone furoate nasal spray on quality of life of patients with acute rhinosinusitis. *Rhinology* 2007;45:190-6.

38. Fokkens WJ, Hoffmans R, Thomas M. Avoid prescribing antibiotics in acute rhinosinusitis.. *BMJ*. 2014;17:349.

39. Hoffmans R, Schermer T, van WC, et al. Management of rhinosinusitis in Dutch general practice. *Prim Care Respir J* 2011;20:64-70.

40. Smith SS, Kern RC, Chandra RK, Tan BK, Evans CT. Variations in antibiotic prescribing of acute rhinosinusitis in United States ambulatory settings. *Otolaryngol Head Neck Surg* 2013;148(5):852-9.

41. Smith SS, Evans CT, Tan BK, Chandra RK, Smith SB, Kern RC. National

burden of antibiotic use for adult rhinosinusitis. *J Allergy Clin Immunol* 2013;132(5):1230-2.

42. Steurer J, Held U, Bachmann LM, et al. Clinical diagnosis of acute bacterial rhinosinusitis, typical of experts. *J Eval Clin Pract* 2009;15:614-9.

43. Sng WJ, Wang DY. Efficacy and side effects of antibiotics in the treatment of acute rhinosinusitis: a systematic review. *Rhinology* 2015;53:3-9.

44. de Kraker ME, Davey PG, Grundmann H.Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med* 2011;8(10):e1001104.

45. Carter D, Charlett A, Conti S, et al. A Risk Assessment of Antibiotic Pan-Drug-Resistance in the UK: Bayesian analysis of an expert elicitation study. *Antibiotics (Basel)* 2017;7:6(1):E9.

46. Babar-Craig H, Gupta Y, Lund VJ. British Rhinological Society audit of the role of antibiotics in complications of acute rhinosinusitis: a national prospective audit. *Rhinology* 2010;48:344-7.

47. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. *Cochrane Database Syst Rev* 2009;(4):CD005149.

48. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol* 2005;116:1289-95.

49. Keith PK, Dymek A, Pfaar O, et al. Fluticasone furoate nasal spray reduces symptoms of uncomplicated acute rhinosinusitis: a randomised placebo-controlled study. *Prim Care Respir J* 2012;21:267-75.

50. 49. Hayward G, Thompson MJ, Perera R, et al. Corticosteroids for the common cold. *Cochrane Database Syst Rev* 2012;15:CD008116.

51. Federspil P, Wulkow R, Zimmermann T. Effects of standardized Myrtol in therapy of acute sinusitis--results of a double-blind, randomized multicenter study compared wi th placebo. *Laryngorhinootologie* 1997;76:23-7.

52. Timmer A, Gunther J, Rucker G, et al. Pelargonium sidoides extract for acute respiratory tract infections. *Cochrane Database Syst Rev* 2008;3:CD006323.

53. Jund R, Mondigler M, Stammer H, et al. Herbal drug BNO 1016 is safe and effective in the treatment of acute viral rhinosinusitis. *Acta Otolaryngol* 2015;135:42-50.

54. Pfaar O, Mullol J, Anders C, et al. Cyclamen europaeum nasal spray, a novel phytotherapeutic product for the management of acute rhinosinusitis: a randomized double-blind, placebo-controlled trial. *Rhinology* 2012;50:37-44.

55. Little P, Stuart B, Francis N, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013; 382(9899):1175-82.

56. Gjelstad S, Høye S, Straand J, et al. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). *BMJ* 2013;347:f4403.

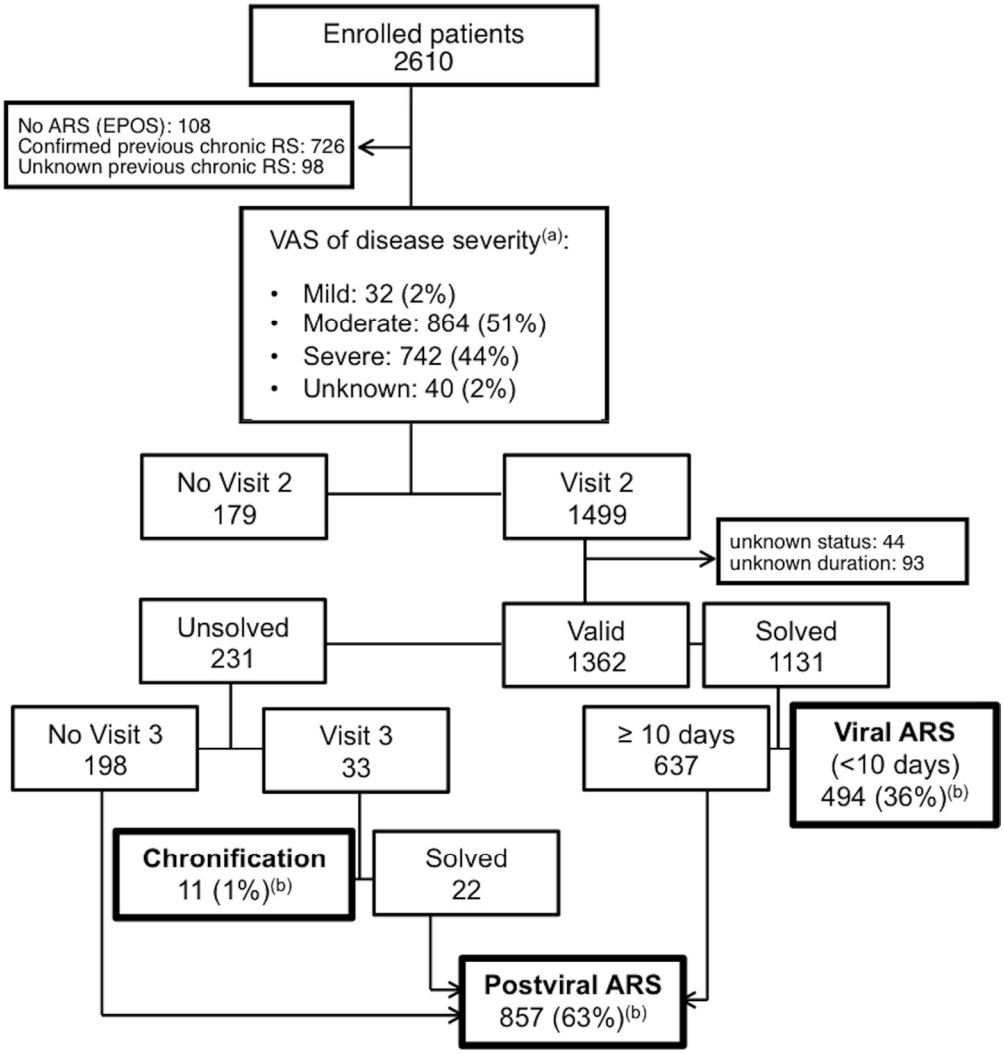

Figure 1

143x152mm (300 x 300 DPI)

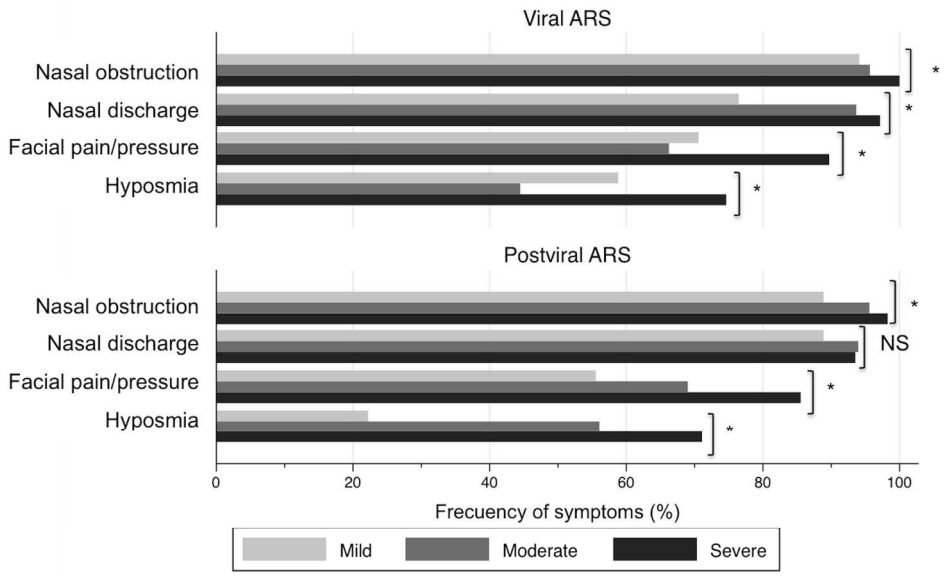

Figure 2

232x162mm (300 x 300 DPI)

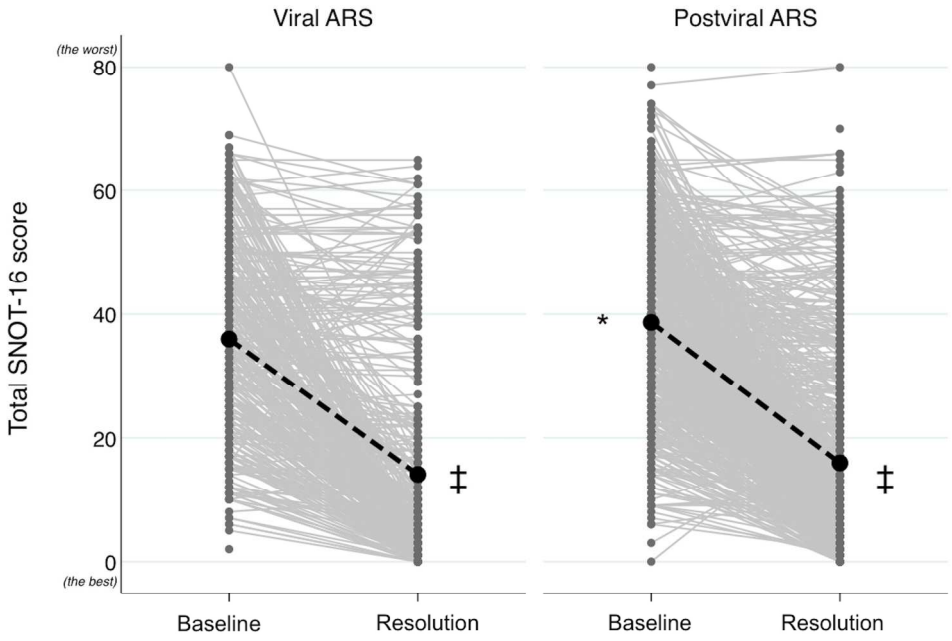

Figure 3

209x152mm (300 x 300 DPI)

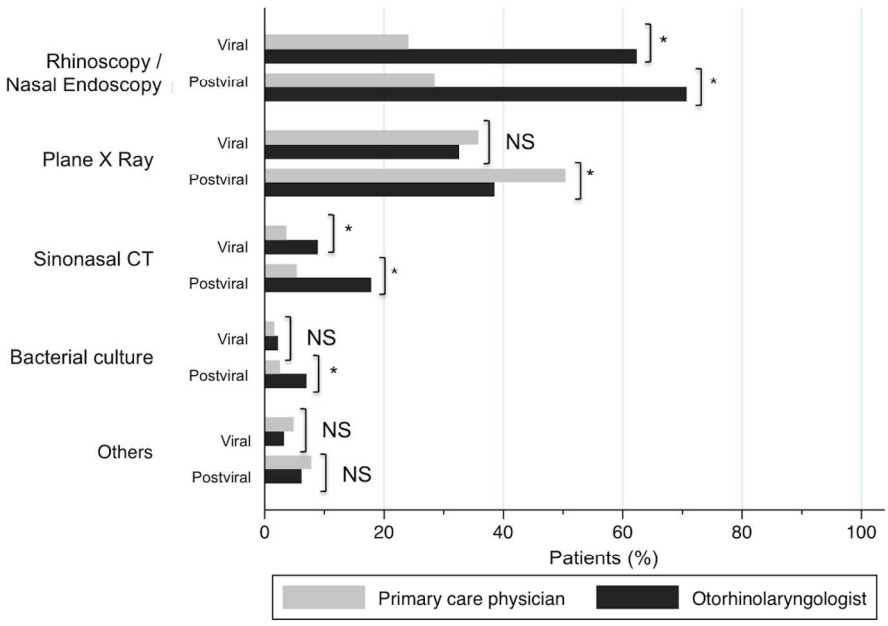

Figure 4

228x152mm (300 x 300 DPI)

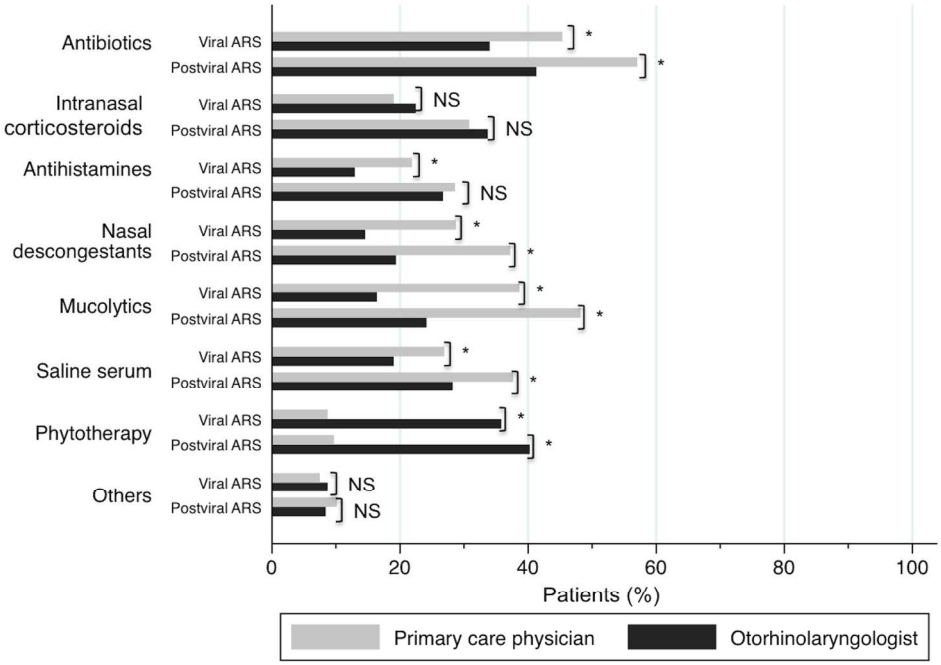

Figure 5

213x152mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract pag 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found pag 3-4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported pag 6-7
Objectives	3	State specific objectives, including any prespecified hypotheses pag 7
Methods		
Study design	4	Present key elements of study design early in the paper pag 8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection pag 8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up pag 8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable pag 8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group pag 9-11
Bias	9	Describe any efforts to address potential sources of bias pag 25
Study size	10	Explain how the study size was arrived at pag 12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why pag 12-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding pag 12-13
		(*b*) Describe any methods used to examine subgroups and interactions pag 12-13
		(*c*) Explain how missing data were addressed The results are derived from a complete case analysis (CC), under the assumption that the missing pattern was Missing At Random (MAR). According to the results from Mukaka et al.[1] recently published in Trials (2016) 17:341 for MAR outcomes, CC method estimates generally remain unbiased and achieve precision similar to or better than Multiple Imputation (MI) methods. However, we would like to point out that we also estimated the multivariate models after MI and obtained very similar results. 1.Rubin, D.B., 1987. Multiple Imputation for Nonresponse in Surveys. John Wiley and Sons, New York.
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses We don't perform any sensitivity analysis. Instead of that we perform the analysis with Multiple Imputation (MI) methods the missing imputation to prove that the results were similar than a complete case analysis.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed pag 14
		(b) Give reasons for non-participation at each stage The flow chart (Fig 1) include the reasons for non-participation at each stage.

		(c) Consider use of a flow diagram Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders pag 14
		(b) Indicate number of participants with missing data for each variable of interest Each table reports the number of participants with data for each variable (Tables 1-5)
		(c) Summarise follow-up time (eg, average and total amount) pag 14
Outcome data	15*	Report numbers of outcome events or summary measures over time pag 14-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included pag 14-19
		(*b*) Report category boundaries when continuous variables were categorized The VAS score to assess severity was categorized as mild, moderate or severe according the paper published by Lim et al. Rhinology 2007. No other continuous variables were assessed.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. We don't use relative risk
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses pag 14-19
Discussion		
Key results	18	Summarise key results with reference to study objectives pag 20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias pag 25
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence pag 20-25
Generalisability	21	Discuss the generalisability (external validity) of the study results pag 26
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based pag 27

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.