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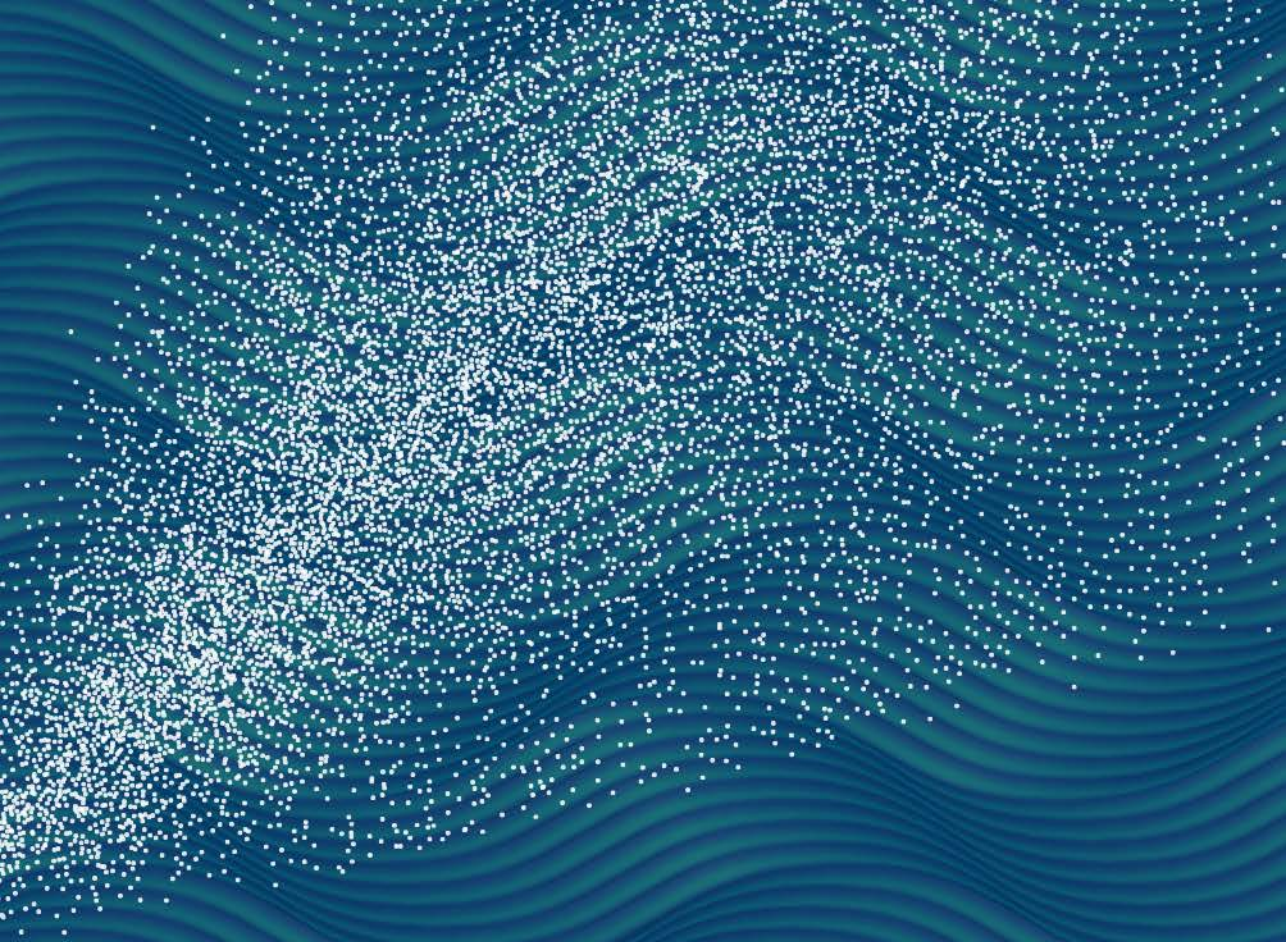

EPIDEMIOLOGY AND MANAGEMENT OF RHINOSINUSITIS

Ruth Hoffmans

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Content

Chapter 1

General introduction

Introduction

Rhinosinusitis

Rhinosinusitis is a common condition in Western countries, leading to a significant burden on society in terms of healthcare consumption and productivity loss [1-4]. However, much remains unknown on its epidemiology and current management. Moreover, clear definitions were lacking until recently, making comparison between various studies (and countries) needlessly hard. Different definitions and words were in use, such as sinusitis and rhinosinusitis. As sinusitis is almost never without rhinitis we prefer rhinosinusitis [5].

In 2012, the European position paper on rhinosinusitis and nasal polyps (EPOS) was published by a multidisciplinary panel including otorhinolaryngologists and general practitioners (GPs) [5]. It reviews what is known about rhinosinusitis and nasal polyps, and it offers evidence-based recommendations on diagnosis and treatment. The paper has been approved by the European Academy of Allergy and Clinical Immunology and the European Rhinologic Society.

EPOS offers clear definitions for rhinosinusitis. It is defined as the presence of two or more sinonasal symptoms one of which should be nasal obstruction or nasal secretions, with or without facial pain/headache and smell dysfunction (epidemiological definition). For the clinical diagnosis, it should be combined with consistent nasal endoscopy and/or CT scans when available [5]. Since the introduction of EPOS, these definitions are used extensively throughout the world [6-8].

Once rhinosinusitis is diagnosed, EPOS further differentiates into acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) based on the duration of symptoms. When symptoms have an acute onset and persist for less than 10 days the condition is defined as common cold/acute (viral) rhinosinusitis. When symptoms increase after 5 days or persist after 10 days but not exceed 12 weeks the condition is defined as acute (postviral) rhinosinusitis. When symptoms are present for more than 12 weeks, the condition is diagnosed as CRS.

Acute rhinosinusitis may be viral or bacterial. Acute bacterial rhinosinusitis is suggested by the presence of at least three symptoms of: discolored discharge and purulent secretion in the cavum nasi, severe local pain, fever above 38°C, elevated ESR/CRP, double sickening (deterioration after initial milder phase; **figure 1**).

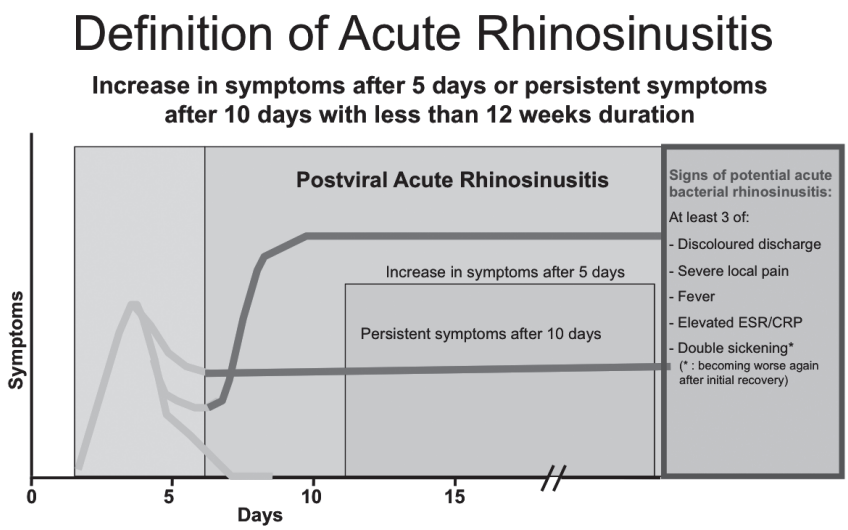

Figure 1. Acute rhinosinusitis in adults [5]

After 12 weeks with symptoms of rhinosinusitis, the condition is defined as chronic rhinosinusitis (CRS). Based on nasal endoscopy, CRS can further be distinguished as CRS with or without nasal polyps (CRSwNP and CRSsNP) [5].

CRS is most likely not a result of prolonged ARS. ARS and CRS are two different entities with their own pathophysiology. The most important differences are that ARS is infectious, short of duration and mostly self-limiting, while CRS is a multifactorial, chronic inflammatory disease. Differentiation between recurrent ARS and CRS can be difficult. In recurrent ARS, patients have complete resolution of their symptoms between episodes. In CRS exacerbations can occur, but symptoms do not resolve completely between these exacerbations (**figure 2**).

Epidemiology

Until now, epidemiological data on rhinosinusitis are limited. The main reason for this was the lack of a clear definition. Since EPOS more and more uni-interpretable data are published [5]. A big player in this field is the Global Allergy and Asthma European Network (GA^{2}LEN), a European network involving over 60 centers in over 20 countries [9,10]. In the next chapters of this thesis epidemiology will be thoroughly discussed.

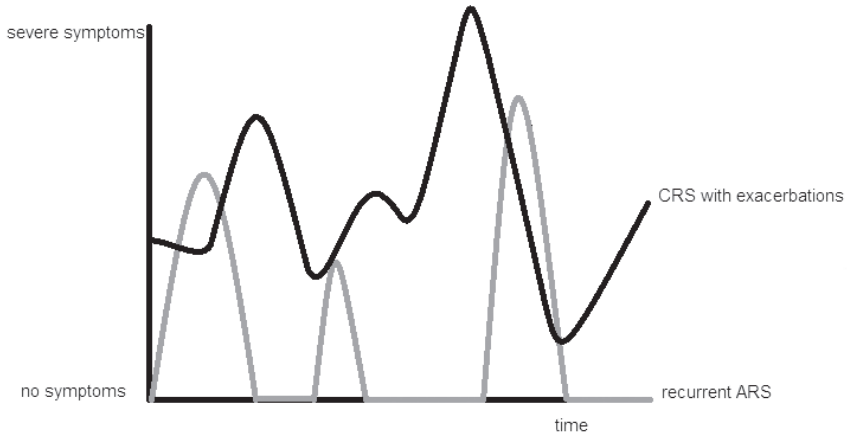

Figure 2. CRS with exacerbations and recurrent ARS

Diagnosis of ARS and CRS

For clinical diagnosis in specialist care some diagnostic tools are used in combination with the mentioned definition.

Nasendoscopy

Endoscopic signs of nasal polyps and/or mucopurulent discharge from middle meatus and/or edema/mucosal obstruction in middle meatus can be seen with nasendoscopy.

Imaging

Plain x-rays and ultrasounds of the sinus have low sensitivity and specificity and are not advised to confirm or rule out a diagnosis of rhinosinusitis. CT scan is the modality of choice. We look for mucosal changes of the ostiomeatal complex and or/sinus. It has to be mentioned that CT is not primary needed to make a diagnosis. In case of unilateral symptoms, in very severe disease, in immune-compromised patients and when complications are expected, CT has to be considered. When scanning a normal population a considerable amount will have incidental abnormalities [5,11].

Management of ARS and CRS

ARS in general practice

Rhinosinusitis is usually managed in primary care; only a small percentage of patients with rhinosinusitis is referred to specialist care. For the management of rhinosinusitis in Dutch general practice a guideline of the Dutch College of General

Practitioners (Nederlands Huisartsen Genootschap, NHG) is frequently used. Until October 2014 this guideline did not distinguish acute from chronic rhinosinusitis. The management of rhinosinusitis was mainly based on the risk of an abnormal course of the disease. It advised treating symptomatically initially. It stated that antibiotics are not indicated for the normal course of rhinosinusitis and that local steroids can be tried in patients with an abnormal course or with recurrences [12]. The new guideline added the word "acute" to rhinosinusitis. This means that only management in case of less than 12 weeks of complaints is discussed. It states that in case of a normal course of the disease education/information and self-support are sufficient. Intranasal corticosteroids are considered in case of no improvement after 14 days or in case of more than 3-4 episodes a year and antibiotics are only indicated in case of a high complication risk [13]. In EPOS a management scheme for acute rhinosinusitis was made for general practitioners (GPs, **figure 3**) [5].

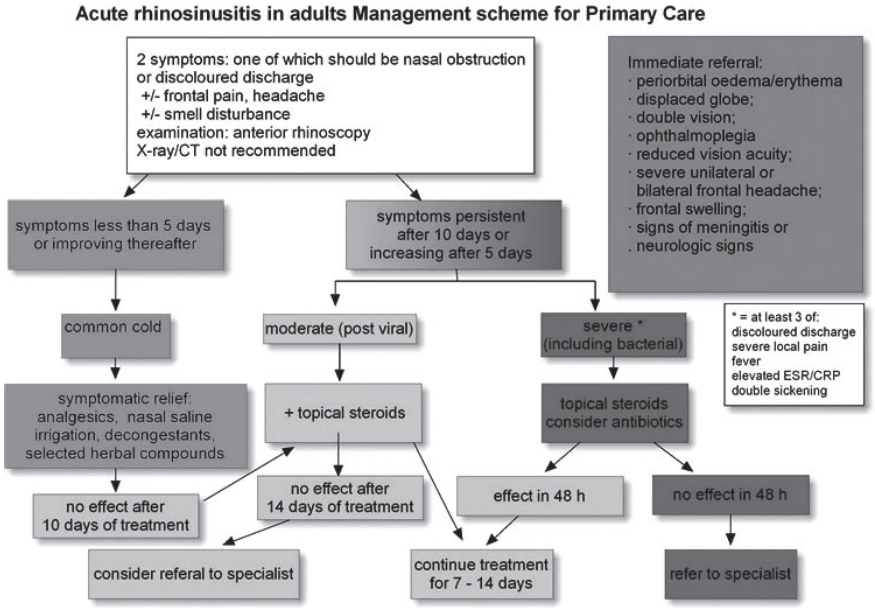

Figure 3. Management of ARS in primary care [5]

CRS in general practice

A separate guideline for chronic rhinosinusitis and nasal polyps has been developed for the Dutch (general) practice, initiated by otorhinolaryngologists and GPs and organised by the "Centraal Begeleidings Orgaan" (CBO) [14]. It advises to start

nasal irrigation with isotonic saline solution. Local corticosteroids are advised in all cases of CRS in primary care. Short-term antibiotics are not advised unless an acute exacerbation occurs. Concerning long-term antibiotics (macrolides) the guideline states that there is insufficient evidence to advise this as an alternative for surgery in patients that do not benefit from local corticosteroids. The possible effect does not outweigh the risk of antimicrobial resistance.

Systemic corticosteroids for 14 days can be considered when there are no contraindications in patients with CRSwNP. Antihistamines are only useful in patients with allergies. A treatment with antileukotrienes can be tried in patients with CRS and asthma.

There is no place for decongestives in the treatment of CRS in primary care according to this guideline [14]. In EPOS there is a clear management scheme for CRS in primary care and non- ENT (ear, nose and throat) specialists (**figure 4**) [5].

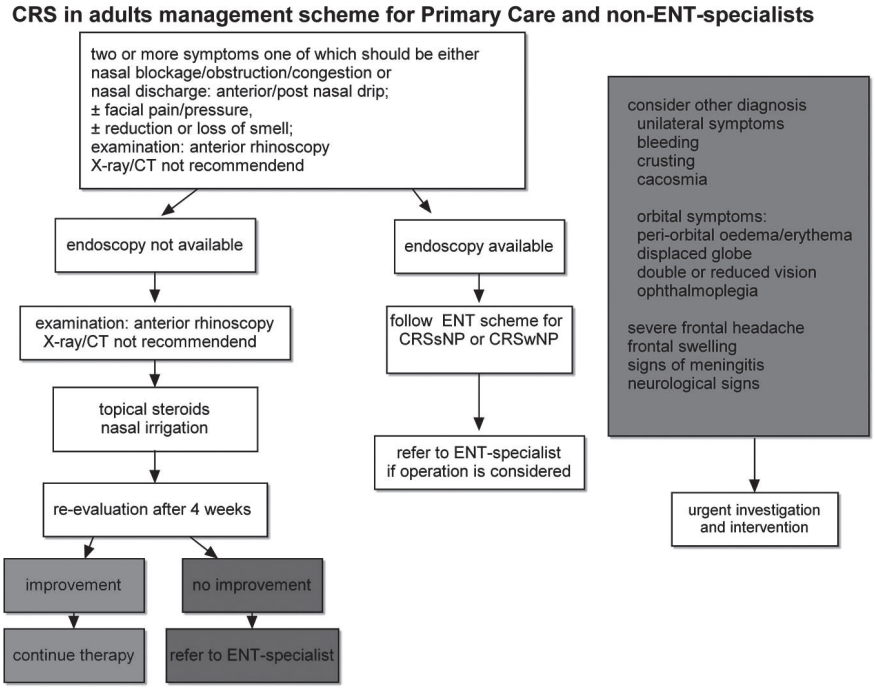

Figure 4. Management of CRS in primary care [5]

ARS in ENT practice

After referral of the GP, ENT-specialists can follow a management scheme as is conducted by EPOS (**figure 5**) [5].

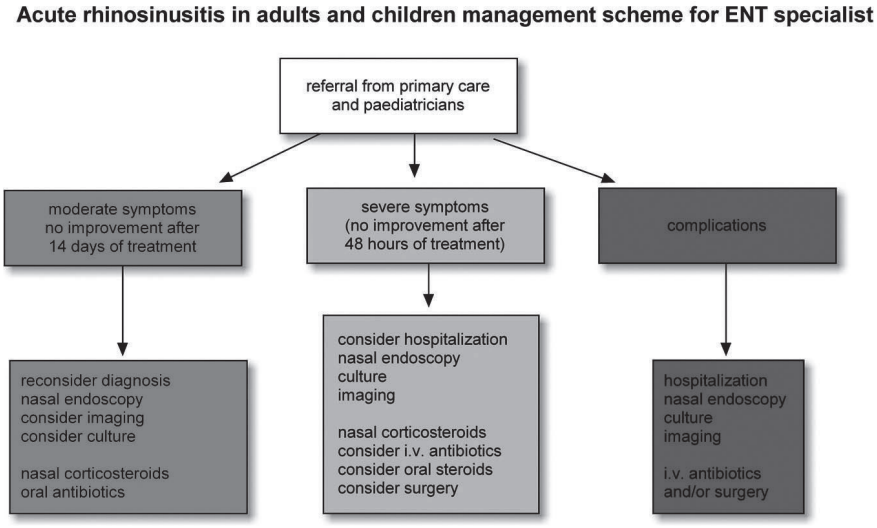

Figure 5. Management of ARS for ENT-specialists [5]

CRS in ENT practice

There are two management schemes for CRS in ENT-practice, one for CRS without polyps (CRSsNP, **figure 6**) and one for CRS with polyps (CRSwNP, **figure 7**).

Surgical treatment

When conservative medical treatment fails in case of ARS and CRS, surgical treatment can be considered. Recently, a panel of experts published what they considered an appropriate medical treatment before considering surgery using an appropriateness methodology. If the 22-item SinoNasal Outcome Test (SNOT-22, a disease specific quality of life test with a possible score between 0 and 110) is scored ≥20 after appropriate treatment and the CT Lund-Mackay score is ≥1 (**figure 8**), surgery is considered a treatment option. In case of CRSwNP topical intranasal corticosteroid (≥ 8 weeks duration) plus a short-course of systemic corticosteroid (1 to 3 week duration) should be tried first. In case of CRSsNP appropriate medical treatment includes topical intranasal corticosteroid (≥ 8 weeks duration) plus either: short course of broad-spectrum/culture-directed systemic antibiotic (2 to 3 weeks duration) or, a prolonged course of systemic low-dose anti-inflammatory antibiotic (≥ 12 weeks duration) [15].

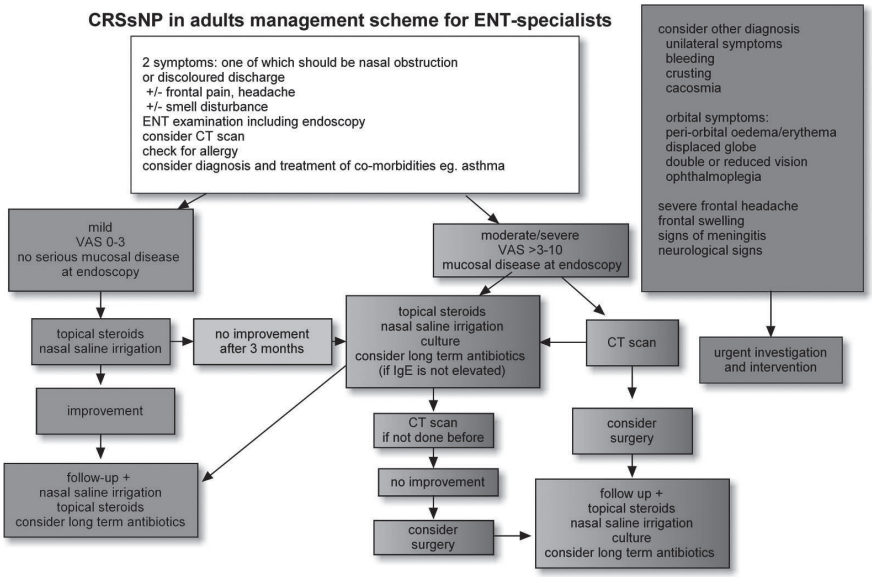

Figure 6. Management of CRSsNP for ENT-specialists [5]

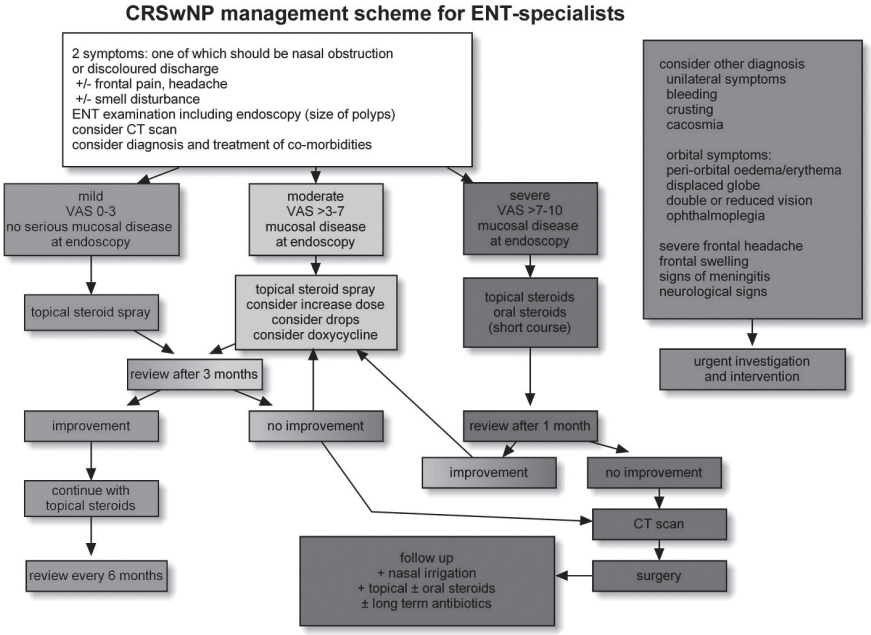

Figure 7. Management of CRSwNP for ENT-specialists [5]

Paranasal sinuses	Right	Left
Maxillary (0,1,2)		
Anterior ethmoid (0,1,2)		
Posterior ethmoid (0,1,2)		
Sphenoid (0,1,2)		
Frontal (0,1,2)		
Ostiomeatal complex (0,2)*		
Total		

Note: 0 - without abnormalities; 1 - partial opacification; 2 - total opacification
* 0 - no obstruction; 2 - obstructed

Figure 8. CT Lund-Mackay score [16]

Endoscopic sinus surgery (ESS) involves the clearance of polyps and polypoid mucosa and inflammatory tissue and opening of the sinus ostia. ESS is superior to extended medical therapy in CRS regarding disease specific quality of life scores and nasal endoscopy scores. ESS is also preferred above polypectomy, Caldwell-Luc, inferior meatal antrostomy and antral irrigations [5,11,17,18].

Possible peroperative complications of ESS are intracranial complications like cerebrospinal fluid leak, orbital complications like hematoma or severe bleeding. Postoperative bleeding, infections and adhesions can occur [5,11,17,18].

Complications of ARS

Orbital complications

Orbital complication can be classified according to Chandler's classification, distinguishing preseptal cellulitis from orbital cellulitis, subperiosteal abscess and orbital abscess (and cavernous sinus thrombosis). Typical signs are conjunctival oedema (chemosis), proptosis, ocular pain, as well as reduced visual acuity and restricted movement of the eye. In some cases initial intravenous antibiotic therapy is sufficient. Indications for surgical drainage are: evidence of subperiosteal or intraorbital abscess on CT or MRI, reduced visual acuity/reduced colour vision/ affected afferent pupillary reflex or inability to assess vision or progressing/not improving orbital signs or general condition after 48 hours of intravenous antibiotic treatment [5,11,19,20].

Intracranial complications

Subdural abscesses, brain abscess, meningitis, encephalitis, and superior sagittal and cavernous sinus thrombosis are possible intracranial complications. Signs of intracranial complications are nausea and vomiting, neck stiffness and altered mental state. Non-specific symptoms like high fever, headache, lethargy, reduced

consciousness, focal neurologic signs or increased intracranial pressure signs can also be signals of an intracranial complication. These complications are treated with high dose, long-term intravenous antibiotics. In many cases this is followed by surgical treatment with burr holes, craniotomy or image guided aspiration.

Osseous complications

Osseous complications result from osteomyelitis of the skull. Most osseous complications are caused by frontal rhinosinusitis, but also other sites may be the origine. These complications may present as Potts Puffy tumour (subperiostal abscess with frontal bone osteomyelitis) or a frontocutaneous fistula. A Potts Puffy tumour presents as a swelling of the forehead in combination with signs of rhinosinusitis. In case of an abscess, surgical treatment is recommended (external approach, endoscopically, burr holes) [11,21].

Recognition and treatment of potential complications is of great importance.

Factors associated with acute and chronic rhinosinusitis

Allergic rhinitis

Allergic rhinitis (AR) is defined as a symptomatic disorder of the nose induced by immunoglobulin E (IgE)-mediated inflammation after allergen exposure of the nasal mucosa. The diagnosis is based on diagnostic tests, such as a skin prick test or measurement of serum specific IgE antibodies in combination with a history of clinical symptoms like sneezing, watery rhinorrhea and nasal blockage. Nasal symptoms can come in combination with eye symptoms and lower airway symptoms [22].

A subdivision in AR can be made in intermittent or persistent rhinitis (less or more than 4 days a week for 4 weeks a year) and mild or moderate/severe rhinitis (based on the impact on quality of life including quality of sleep, the feasibility of daily activities, functioning in school and work, and the level of troublesomeness of symptoms) [22].

Asthma

Asthma is a chronic disease with bronchial inflammation with prominent eosinophil infiltration. It is characterized by recurrent attacks of breathlessness/ chest tightness and wheezing or cough [23,24]. The mucosa of the lower airway is in continuum with the upper airway, a so called unified airway [22,25-28]. When treating asthma, rhinosinusitis usually gets milder and the other way around [25].

Aspirin intolerance

Intolerance reactions to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported with different incidence rates. In the general population it is 0,6-2,5% and even higher in asthmatics. A combination of nasal polyps with asthma (exacerbating after intake of NSAIDs) and sensitivity to NSAIDs was previously known as the Samter or ASA triad. A new definition has been proposed by Kowalski et al.: NSAIDs-exacerbated respiratory disease, NERD [29]. When operated, the recurrence rate of polyps is higher in populations with aspirin intolerance than in populations without aspirin intolerance [5,11].

Smoking

Current smoking is found to be correlated to an increased prevalence of CRS [9,10,30]. The relation between smoking and ARS is unknown.

Orodontal disease

The position of the maxillary teeth in the floor of the maxillary sinus declares that maxillary rhinosinusitis is potentially caused by dental infection. Odontogenic rhinosinusitis seems to increase in the United Kingdom [31].

Environment

Environment has been found to be of influence on upper respiratory disease in some studies [32,33]. Sundaresan et al., evaluating 41 articles on occupational and environmental influences on CRS, state that the current literature allows us to make very few conclusions about the role of hazardous occupational or environmental exposures in CRS [34].

Aims of this thesis

We would like to give an overview of the epidemiology and management of ARS and CRS in the Netherlands.

To start with the prevalence of these diseases in the general population, including patients that did not visit their GP for their complaints. They are not registered with a diagnosis in any registration system and remain unknown if we do not specifically look for them. We would like to find out which persons are at risk for ARS and CRS and whether the place of residence is of influence on the prevalence of these diseases. Maybe a rural environment has another impact on ARS and CRS than an urban environment.

An epidemiological study based on questionnaires can only be based on self-reported symptoms. We wanted to know whether self-reported symptoms of CRS are suitable for the assessment of geographic variations in prevalence of CRS.

Furthermore, we would like to assess the incidence of ARS and CRS in primary care. In Dutch primary care a few morbidity registrations exist in which GPs register their diagnoses and patient characteristics and sometimes their management. This, we thought, was very useful to reach our goal to assess the incidence and management of ARS and CRS by GPs.

To not only trust on GPs that participate in morbidity registrations, a random sample of GPs in the Netherlands filled out our questionnaire on the diagnosis and management of ARS and CRS. The Dutch guideline for GPs on rhinosinusitis advises GPs in their management, but do they follow this guideline, or do they have their own preferences?

When the GP refers to a hospital in case of complicated rhinosinusitis, sometimes antibiotics are started before referral. More and more restraint is advised in prescribing antibiotics in case of rhinosinusitis. But do they influence the occurrence of these complications? Do we have to avoid prescribing antibiotics or are they important in prevention of complications?

In the remainder of this thesis, these questions will be answered.

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Chapter 2

Rhinosinusitis in the general population

Chapter 2.1

Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment

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Abstract

Background

This study was conducted to assess the effect of comorbidity, ethnicity, occupation, smoking and place of residence on allergic rhinitis (AR), acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS).

Methods

A GA^{2}LEN (The Global Allergy and Asthma European Network) screening questionnaire was sent to a random sample of the Dutch population (n=16700) in three different areas of the Netherlands.

Results

Fifty percent (8347) of the questionnaires sent were returned. A total of 29% respondents (27-31% in different areas) met the criteria for AR, 18% (17-21%) for ARS and 16% (13-18%) for CRS. Risk factors for AR were itchy rash, eczema, adverse response after taking a painkiller, asthma, CRS and ARS. Moreover, the risk of AR was twice as low for full-time housewives/househusbands than for people with jobs. The risk of ARS or CRS was significantly higher in respondents with a doctor's diagnosis of CRS, AR, itchy rash or smoking. The risk of CRS was also significantly higher in respondents with an adverse response after taking painkillers, active smoking or asthma. Caucasians are generally less likely to have AR or CRS than Latin-Americans, Hindustani and African-Creoles, and more likely to have ARS than Asian, Hindustani, Mediterranean and African-Creoles.

Conclusions

This study found shared and distinct risk factors for AR, ARS and CRS and therefore provides support for the belief that they have shared symptoms but are different diseases with different aetiologies.

Introduction

Allergic rhinitis (AR), acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) are common upper airway diseases [1-4]. According to the European position paper on rhinosinusitis and nasal polyps (EPOS), rhinosinusitis is clinically defined as inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and/or facial pain/pressure and reduction or loss of smell, combined with objective signs of disease identified by endoscope or CT scan. The definition without objective signs is used in epidemiological studies. When the onset of these symptoms is acute and when they are present for less than twelve weeks, the diagnosis is ARS. When they persist for more than twelve weeks, the diagnosis is CRS [2].

AR is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation of the nasal membranes. The symptoms include rhinorrhoea (anterior or posterior), nasal congestion, nasal itching, and sneezing [5]. There is no uniform definition for epidemiological studies. Different definitions have been used in questionnaires in previous studies [5,6].

There is a lot of data about the effect of comorbidity (eczema, urticaria and asthma, for example), ethnicity, occupation, smoking and place of residence on the incidence of AR [5], but less is known about the effect of these factors on CRS[2] and little is known about ARS.

The GA[2]LEN survey was conducted under the auspices of The Global Allergy and Asthma European Network (GA[2]LEN). The associated questionnaire was designed to focus specifically on upper airway symptoms and particularly upper airway disease like rhinitis and rhinosinusitis, but also on some gaps in our scientific understanding of allergic disease and some risk factors such as adverse response to painkillers, occupation, ethnicity, smoking exposure, age and gender.

There are theories about the association between AR and ARS and CRS. One theory is that allergy causes swelling of the mucosa, which obstructs the ostium of the sinuses and impairs mucocilliary transport, and possibly induces rhinosinusitis [2]. Another theory argues that there is significantly more inflammation (eosinophils) in the maxillary sinus of allergic patients during the season than out of season [7,8]. Pathophysiological processes that involve the upper airway generally affect lower airway disease. Mucosa in the ear, nose, sinus and lower airways is often inflamed at the same time. The majority of patients with asthma also have allergic rhinitis. Support for the unified airway theory is found in epidemiological studies, in shared pathophysiological mechanisms, and in interactive treatment effects [5,9-11].

We wanted to look at whether different areas (with different levels of air pollution) in the Netherlands (Amsterdam and the east of the Netherlands) and/or ethnicity could play a role in the prevalence and severity of ARS , CRS and AR. This study was conducted to assess the relationships between AR, ARS and CRS and comorbidity, ethnicity, occupation, smoking and place of residence.

Methods

Study design

Most of the data for the present study were obtained using the GA^{2}LEN questionnaire, which consists of 22 questions. The questionnaire was sent to a random sample of the Dutch population in three different areas of the Netherlands (**Figure 1**) with different geographic locations, housing, population densities, ethnic profiles:

1. Ouderkerk aan de Amstel, a suburban village close to Amsterdam (545 inhabitants/km^2): 5000 questionnaires
2. Amsterdam South East, an urban area with many different ethnicities (4704 inhabitants/km^2) 6700 questionnaires
3. Almelo, a city in a more rural area in the east of the Netherlands (1077 inhabitants/km^2): 5000 questionnaires

Figure 1. Map of the Netherlands with the three different areas

In the surveys in Amsterdam and Almelo (sent in 2009), we included extra questions about acute rhinosinusitis (ARS) and ethnicity alongside the questions about chronic rhinosinusitis (CRS) and allergic rhinitis (AR).

The questionnaire can be found in the appendix. We sent it up to three times if there was no response.

Relevant definitions based on the questions in the questionnaire

AR: a positive answer to the question:

Do you have any nasal allergies including hay fever?

ARS: a positive answer to the question:

In the past twelve months, did you have at least one episode of at least ten days with a blocked nose, discoloured nasal discharge and pain or pressure in the sinuses?

CRS: A combination of two positive answers to the next questions (with at least a positive answer to either A or B):

A. Has your nose been blocked for more than twelve weeks in the last twelve months?

B. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat for more than twelve weeks in the last twelve months?

C. Have you had pain or pressure around the forehead, nose or eyes for more than twelve weeks in the last twelve months?

D. Has your sense of smell been reduced or absent for more than twelve weeks in the last twelve months?

A doctor's diagnosis of CRS: a positive answer to the question:
Has a doctor ever told you that you have chronic sinusitis?

Itchy rash: a positive answer to the question:
Have you ever had an itchy rash that came and went for at least six months?

Eczema: a positive answer to the question:
Have you ever had eczema or any kind of skin allergy?

Adverse response after taking painkillers: a positive answer to the question:
Have you ever had any difficulty with your breathing within three hours after taking a painkiller?

Active smoking: a positive answer to the questions:
Have you ever smoked for as long as a year? AND Have you smoked at all in the last month?

Asthma: a positive answer to the question:

Have you ever had asthma? AND one of the following:

- Have you had wheezing or whistling in your chest at any time in the last twelve months?
- Have you woken up with a feeling of tightness in your chest at any time in the last twelve months?
- Have you been woken by an attack of shortness of breath at any time in the last twelve months?
- Have you been woken by an attack of coughing at any time in the last twelve months?

Ethics statement

Our institutional review board (ethics committee) decided that their approval was not needed to start this study because participants were not subject to any intervention.

Statistical analysis

Statistical analyses were conducted with SPSS 21.0 statistical software.

Univariate statistical analyses for all the different variables in each area were completed. The percentages were calculated using the frequencies and total available data for each area and variable (without missing values). Significant differences between the areas were calculated using Chi-square or ANOVA (Analysis of variance) for each variable.

Univariate analysis was then conducted for the three outcome variables ARS, CRS and AR using Pearson chi-square or t-test depending on binary or continuous data for each variable. The independent variables with a p-value of less than 0.20 in the univariate analysis were selected for multivariate analysis. Multivariate logistic regressions were fitted by using the backward elimination technique based on likelihood ratio to identify factors that affect ARS, CRS and AR separately. The association between independent variables was assessed using odds ratio (OR) and a 95% confidence interval (CI). Correlations were considered to be significant if the p-value was less than 0.05.

Results

Fifty percent (8347) of the 16700 questionnaires sent were returned (**Table 1**). The mean age of the respondents was 46 years (range 6-90); 45% were male.

Univariate analysis

Table 2 summarises the results of the univariate analysis.

A total of 2274 respondents met the criteria for ARS, of whom 841 also met the criteria for CRS. Those 841 patients were excluded from the ARS group since they will have answered 'yes' to this question given their CRS. The prevalence of ARS is

Table 1. Respondents

Area	Sent	Respondents	Percentage
Ouderkerk a/d Amstel	5000	3192	64
Amsterdam SE	6700	2586	39
Almelo	5000	2569	51
Total	16700	8347	50

therefore 18% (1433/8170). The prevalence of CRS was 16% (1281/8227). In total, 29% (2259/7804) of the respondents met the criteria for AR.

All variables were compared for the different areas. AR, ARS, itchy rash, adverse response to painkillers, smoking (active and at least one year), occupation, ethnicity, CRS, asthma and age differed significantly between the areas.

Table 2. Summary of results (univariate)

	Amsterdam SE N (%)	Almelo N (%)	Ouderkerk N (%)	Total N (%)	P
Allergic rhinitis	750 (31) $	699 (29)	810 (27)	2259 (29)	0.005
Doctor's diagnosis CRS	104 (4)	94 (4)	108 (3)	306 (4)	0.366
ARS	368 (17) #,$	469 (21)	596 (20)	1433 (18)	0.000
Itchy rash	622 (25) $	601 (24) &	612 (20)	1835 (23)	0.000
Eczema	1095 (45)	1108 (45)	1283 (43)	3486 (44)	0.245
Adverse response painkiller	56 (2) $	54 (2) &	36 (1)	146 (2)	0.002
Smoking (1 year)	1164 (47) #,$	1319 (52) &	1563 (50)	4046 (50)	0.000
Smoking (active)	595 (43) $	630 (44) &	695 (32)	1920 (39)	0.000
Occupation					0.000
Employed	1389 (56) #,$	1283 (52)	1672 (53)	4344 (54)	0.023
Self-employed	117 (5) #,$	153 (6) &	360 (11)	630 (8)	0.000
Unemployed	94 (4) #,$	55 (2) &	40 (1)	189 (2)	0.000
Not working because of poor health	128 (5) $	101 (4) &	67 (2)	296 (4)	0.000
Full time house person	101 (4) #,$	207 (8) &	201 (6)	509 (6)	0.000
Full time student	215 (9) $	193 (8)	230 (7)	638 (8)	0.276
Retired	312 (13) #,$	393 (16)	481 (15)	1186 (15)	0.001
Other	111 (5)	97 (4)	119 (4)	327 (4)	0.495
Ethnicity					0.000
Caucasian	1293 (56) #	1799 (86)		3092 (70)	0.000
Asian	141 (6)	104 (5)		245 (6)	0.108
African-Creole	354 (15) #	12 (1)		366 (8)	0.000
Latin-American	59 (3) #	4 (0,2)		63 (1)	0.000
Hindustani	206 (9) #	7 (0,3)		213 (5)	0.000
Mediterranean	45 (2)	53 (3)		98 (2)	0.182
Other	225 (10) #	117 (6)		342 (8)	0.000
Gender (female)	1453 (57) #	1361 (53)	1748 (55)	4562 (55)	0.058
CRS	450 (18) $	420 (17) &	411 (13)	1281 (16)	0.000
Asthma	185 (8) $	208 (9) &	185 (94)	578 (7)	0.000
Age (mean)	45.4 $	46.5 &	47.0		0.000

# significant difference between Amsterdam Southeast and Almelo
$ significant difference between Amsterdam Southeast and Ouderkerk aan de Amstel
& significant difference between Almelo and Ouderkerk aan de Amstel

Multivariate analysis

ARS

The risk of ARS was significantly higher in respondents with a doctor's diagnosis of CRS (OR 2.14), AR (OR 1.70), itchy rash (OR 1.28) and eczema (OR 1.33), in female respondents (OR 1.39) or those with a history of smoking for at least one year (OR 1.22). Caucasians have a significantly higher risk of ARS than people of most other ethnicities in our survey. Getting older reduces the risk of ARS by an OR of 0.99 per year. **Table 3** shows all variables significantly related to ARS. No significant relation with work/occupation or place of residence was found.

Table 3. Variables related to ARS (multivariate)

Variable	p	OR	95% CI-	95% CI
Doctor's diagnosis CRS	0.01	2.14	1.17	3.91
AR	0.00	1.70	1.38	2.10
Gender (ref: male)	0.00	1.39	1.14	1.69
Eczema	0.01	1.33	1.08	1.65
Itchy rash	0.04	1.28	1.01	1.62
Smoking (1 year)	0.05	1.22	1.00	1.50
Age (per year)	0.05	0.99	0.99	1.00
Ethnicity (ref: Caucasian)	0.00			
Other	0.10	0.74	0.52	1.06
Latin-American	0.26	0.54	0.18	1.59
Asian	0.00	0.45	0.26	0.76
Hindustani	0.00	0.40	0.22	0.74
Mediterranean	0.04	0.40	0.17	0.95
African-Creole	0.00	0.35	0.21	0.59

CRS

The risk of CRS is significantly higher in respondents with a doctor's diagnosis of CRS (OR 6.83), AR (OR 2.87), asthma (OR 2.36), an adverse response after taking painkillers (OR 2.34), itchy rash (OR 1.71), or active smoking (OR 1.45). Caucasians were less likely to meet the criteria for CRS than people with some other ethnicities (African-Creole, Latin-American, Hindustani). CRS is also less likely in older patients. No significant relation was found with work/occupation, place of residence or gender. **Table 4** shows the variables significantly associated with CRS.

Table 4. Variables related to CRS (multivariate)

Variable	p	OR	95% CI-	95% CI
Doctor's diagnosis CRS	0.00	6.83	3.91	11.94
AR	0.00	2.87	2.11	3.81
Adverse response painkiller	0.01	2.34	1.20	4.54
Asthma	0.00	2.36	1.52	3.66
Itchy rash	0.00	1.71	1.26	2.31
Smoking (active)	0.01	1.45	1.08	1.95
Age (per year)	0.02	0.99	0.98	1.00
Ethnicity (ref: Caucasian)	0.00			
Latin-American	0.05	3.56	1.01	12.51
African-Creole	0.00	2.53	1.52	4.20
Hindustani	0.04	2.04	1.04	4.01
Mediterranean	0.20	1.77	0.74	4.26
Asian	0.10	1.74	0.90	3.37
Other	0.35	0.75	0.42	1.36

AR

The risk of AR was significantly higher in respondents with an adverse response after taking a painkiller (OR 4.12), asthma (OR 3.24), CRS (OR 2.24) or a doctor's diagnosis of CRS (OR 2.29), ARS (OR 1.74), eczema (OR 1.60), or itchy rash (OR 1.43). Active smokers were less likely to have AR (OR 0.74). Full-time housewives/househusbands were significantly less likely to have AR than respondents in employment (OR 0.46). Caucasians generally were less likely to have AR than African-Creoles, Latin-Americans and Hindustanis. Once again, the risk of AR declined with increasing age and no significant relation was found with gender or place of residence. **Table 5** lists the variables related to AR.

Table 5. Variables related to AR (multivariate)

Variable	p	OR	95% CI -	95% CI
Adverse response painkiller	0.00	4.12	1.71	9.93
Asthma	0.00	3.24	1.98	5.31
Doctor's diagnosis CRS	0.04	2.29	1.04	5.04
CRS	0.00	2.24	1.34	3.73
ARS	0.00	1.74	1.29	2.35
Eczema	0.00	1.60	1.20	2.13
Itchy rash	0.02	1.43	1.05	1.96
Age (per year)	0.00	0.98	0.97	0.99
Smoking (active)	0.03	0.74	0.56	0.97
Ethnicity (ref: Caucasian)	0.01			
Latin-American	0.03	5.13	1.16	22.70
Hindustani	0.02	2.35	1.15	4.80
African-Creole	0.01	1.97	1.14	3.37
Mediterranean	0.29	1.60	0.67	3.83
Other	0.12	1.45	0.90	2.33
Asian	0.73	1.13	0.57	2.23
Occupation (ref: employed)	0.08			
Unemployed	0.20	1.58	0.78	3.21
Retired	0.66	1.12	0.68	1.83
Not working because of poor health	0.82	1.07	0.59	1.97
Self-employed	0.71	0.90	0.53	1.55
Full-time student	0.10	0.57	0.29	1.12
Other	0.14	0.55	0.25	1.22
Full-time housewife/husband	0.02	0.46	0.24	0.87

Discussion

We evaluated the risk factors for AR, ARS and CRS in an epidemiological study looking at three different locations in the Netherlands.

Most studies in the past have asked subjects whether they had 'sinusitis' (diagnosed by a doctor), often without distinguishing between ARS and CRS [12-14]. The present

study used the GA²LEN questionnaire and so we were able to distinguish between ARS and CRS on the basis of symptoms reported by the patients and a possible doctor's diagnosis of CRS.

A doctor's diagnosis of CRS and the diagnosis CRS based on symptoms are obviously related (OR 2.29). But not all participants with symptom based CRS have a doctor's diagnosis. They may be less care seeking or they may have less severe complaints. Also in the Dutch healthcare system, general practitioners are not always aware of the difference between acute and chronic rhinosinusitis [15,16]. Therefore the participants that did go to their general practitioner did probably only hear a diagnosis of "sinusitis" and not "chronic rhinosinusitis".

The strength of symptom based diagnosis of CRS is that participants that are not aware of their diagnosis can be found. We realise that we are not always able to distinguish perfectly between the different diseases: persistent AR and CRS, for example, are not always easy to separate on the basis of symptoms alone [17]. However, using the same GA²LEN questionnaire, Tomassen et al. found that 62% of the subjects reporting CRS on the basis of symptoms also had objective abnormalities at endoscopy [18]. A Korean study correlated all the different combinations of CRS symptoms with the findings of nasal endoscopy and found that all combinations with a reduction or loss of smell had the highest OR for a positive endoscopy [19].

The strength of doctor's diagnosed CRS is that a professional has combined symptoms and objective findings to make a diagnosis. However part of the patients will not visit their doctor and some doctors will not recognize CRS, leading to an underestimation of the prevalence of CRS.

We have to keep in mind that there may be a participation bias. Individuals with nasal and sinus symptoms are more likely to respond to a questionnaire about these symptoms than individuals without these symptoms. Therefore the prevalence may be overestimated. The prevalence found in this study was slightly higher than reported for the Netherlands on the basis of the Ouderkerk data only (CRS 14.3%) and also confirms the relatively high prevalence of CRS in the Netherlands by comparison with the average in Europe (11%) [20] and the US (12%) [21].

We also realise that some of the subjects reporting allergies tested negative in skin-prick testing and that others were not aware of the allergic basis for their complaints. In an Italian study, 79% of the participants reporting AR had either a positive skin prick test or at least one specific IgE measurement ≥ 0.35 kU/l [22]. Twenty-eight percent of the participants in a Turkish study who answered 'yes' to the question 'Do you have or have you ever had any nasal allergies, including hay fever?' had a positive skin prick test [23].

The associations found between AR, ARS, CRS and asthma and eczema concur with other studies evaluating the comorbidities of AR [24,25].

We found that Caucasians were less likely to have AR than most other ethnicities. In an English study in general practice, significantly fewer Southern Irish participants and significantly more West Indian women consulted a general practitioner for AR than the native British population [26]. By contrast, Salo et al. found that non-Hispanic whites reported more hay fever than non-Hispanic blacks, Mexican Americans and other ethnicities [27].

Interestingly, we found that full-time housewives/househusbands were significantly less likely to have AR than respondents with jobs. This is a new finding that could possibly be explained by occupational AR in the latter group. It is known that occupational exposure is related to upper airway disease [28]. Occupational AR may result from a wide variety of high-molecular-weight agents and some low-molecular-weight agents. Examples of occupations at increased risk are furriers, bakers, livestock breeders, food-processing workers, veterinarians, farmers, electronic/electrical products assemblers and boat builders [29-31]. Furthermore, AR has been found be more prevalent in medical professionals than in office workers and in cleaners [32,33].

Occupational status might reflect socioeconomic status and may be of influence on the prevalence of ARS, CRS and AR. In a recent study by Philpott factors such as occupation, highest academic qualification, rural/urban location, duration of residency, proximity to crops, postcode, annual income, ethnicity, household occupancy and social class were studied in relation to CRS. No significant differences were found after adjusting for age and sex [34].

Hirsch used the history of receiving Medical Assistance as surrogate for socioeconomic status and found that this was associated with CRS [21].

Kilty found that participants with an educational level of high school or less report higher sinus symptom scores than participants with post-secondary education. Their Lund MacKay score on CT however is not significantly different [35]. This indicates that socioeconomic factors may be of influence on reporting of (severity) of symptoms. Unfortunately, we do not have information about the socioeconomic status of our participants.

Conflicting results have been found in previous studies about the effect of smoking on AR [5,27,36-39]. In our study, we found a negative association between smoking and AR. The healthy smoker phenomenon could explain why our study and some other studies have shown that smokers are less likely to have AR than non-smokers [5,36-38].

It is possible that allergy subjects are less likely to start smoking and more likely to quit smoking. Smoking may have an immunosuppressive effect and reduce the number of IgE sensitizations [27,39].

In our multivariate analysis, we did not find any association between place of residence and AR. However, several studies have found a link between living environment and nasal symptoms/AR. People living close to heavy traffic and in cities reported nasal symptoms more often [40-42]. It is very probable that the wide range of living conditions in the three locations was such that these differences could not be found.

The present survey confirmed the findings in the literature indicating a significant correlation between asthma and CRS and AR, but not between asthma and ARS [43-46]. This could be explained by the fact that CRS and AR are chronic diseases, as is asthma. The finding supports the unified airway theory and the conclusion that ARS and CRS are two different diseases.

The relation of an adverse response to painkillers and CRS (with nasal polyps) is not surprising because they often occur together with asthma as part of AERD (aspirin-exacerbated respiratory disease) [2]. Itchy rash as defined in our study might fit the diagnosis of urticaria.

When we look at the relation of urticaria with ARS and CRS in other studies, we found that chronic urticaria are often related to infections (in general) in several studies [47-50]. Positive nasal swabs were more often found in patients with urticaria than in controls [48].

In this study, Caucasians tended to have a higher prevalence of ARS and a lower prevalence of chronic respiratory conditions as CRS and AR by comparison with other ethnicities. It is difficult to compare these data with previous studies because of differences in the definitions of race/ethnicity and rhinosinusitis (ARS and CRS were not studied separately elsewhere). Our data confirm an earlier study by Tan, in which the local population of Singapore had more CRS than the Caucasian population. The local population of Singapore consisted of Chinese (71.2%), Malay (8.9%), Indian (13.5%) and other ethnicities (6.6%) [51]. A survey from the US found associations between the prevalence of rhinosinusitis (defined as a positive response to the question: 'During the past twelve months, have you had sinusitis or sinus problems?') and female gender, non-Hispanic white or black race, higher income status and higher educational level [12]. Contrary to our data, Hirsch et al. found that non-whites had a lower risk of meeting the EPOS CRS criteria than whites in the United States (OR 0.53) [21].

We found that women were more likely to have ARS, but not CRS. This concurs with the study by Hirsch [21]. Almost 15% of the respondents from the 2002-2005 National Health Interview Survey of the United States had been diagnosed with rhinosinusitis in the previous year (doctor's diagnosis, no differentiation between ARS and CRS). This prevalence was lower in the Asian (7%) and Hispanic populations (8.6-8.8%) than in the black population (13.3-14.4%) and the white population (13.0-16.0%) [13,14]. In a retrospective study in children it was found that there were more white children in the CRS group (77%) than in the group without CRS (47%). (CRS group: 77% white, 10% black, 13% other; control group: 47% white, 33% black, 20% other) [52]. Different study types with different populations and different definitions of ethnicities and rhinosinusitis may explain the conflicting findings on this subject. It may be a genetical issue, but habits/environment may also play a role. Further research is needed to elucidate the findings regarding ethnicity in our study. We did not find any significant association between CRS and work/occupation. Earlier, Thilsing et al. did find an increased prevalence of CRS in subjects working in a cleaning job [53]. A correlation has also been found between occupational exposure to low- and high-molecular-weight irritants and the number of FESS (functional endoscopic sinus surgery) procedures in patients with CRS [54]. However, a recent review by Sundaresan evaluating 41 articles that discussed occupational and environmental influences on CRS stated that the literature at present allows us to draw very few conclusions about the role of hazardous occupational or environmental exposures in CRS, leaving a critical knowledge gap regarding potentially modifiable risk factors for disease onset and progression [55]. More research is definitely needed to elucidate the effect of occupational exposure on CRS.

We found a positive link between smoking and CRS and ARS, confirming other studies [3,12,21,53,54].

In conclusion, this study found new associations between different upper airway diseases and relevant factors. It is again clear that chronic upper airway diseases like AR and CRS are associated with other factors than acute diseases like ARS.

More studies are required evaluating sensitisation and other objective signs of disease to further unravel these observations.

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Appendix

GA²LEN survey questionnaire

TIP

	NO	YES
TO ANSWER THE QUESTIONS PLEASE TICK THE APPROPRIATE BOX		√
IF YOU ARE UNSURE OF THE ANSWER PLEASE CHOOSE 'NO' 		

NO YES

1. Have you had wheezing or whistling in your chest at any time **in the last 12 months**?

*IF '**NO**' GO TO QUESTION 2* *IF 'YES' GO TO QUESTION 1.1*

NO YES

1.1 Have you been at all breathless when the wheezing noise was present?

NO YES

1.2 Have you had this wheezing or whistling when you did not have a cold?

NO YES

2. Have you woken up with a feeling of tightness in your chest at any time **in the last 12 months**?

NO YES

3. Have you been woken by an attack of shortness of breath at any time **in the last 12 months**? ☐ ☐

NO YES

4. Have you been woken by an attack of coughing at any time **in the last 12 months?** ☐ ☐

NO YES

5. Do you bring up phlegm from your chest on most days for as much as three months each year? ☐ ☐

NO YES

6. Have you **ever** had asthma? ☐ ☐

IF 'NO' GO TO QUESTION 7 ***IF 'YES' GO TO QUESTION 6.1***

YEARS

6.1 How old were you when you had your first attack of asthma? (If unsure, give your best guess!) ☐☐

NO YES

6.2 Have you **ever** been hospitalised with asthma? ☐ ☐

NO YES

6.3 Have you had an attack of asthma **in the last 12 months?** ☐ ☐

NO YES

6.4 Are you **currently** taking any medicine (including inhalers, aerosols or tablets) for **asthma?** ☐ ☐

NO YES

7. Do you have any nasal allergies including hay fever?

IF 'NO' GO TO QUESTION 8

IF 'YES' GO TO QUESTION 7.1

NO YES

7.1 Have you been troubled by nasal allergies **in the last 12 months?**

NO YES

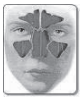
7.2 Have you ever been troubled by nasal allergies for **more than 4 days in any one week**?

NO YES

7.3 If yes did this happen for **more than 4 weeks continuously?**

NO YES

8. Has your nose been blocked **for more than 12 weeks during the last 12 months?**



NO YES

9. Have you had pain or pressure around the forehead, nose or eyes **for more than 12 weeks during the last 12 months?**

NO YES

10. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat **for more than 12 weeks during the last 12 months?**

NO YES

11. Has your sense of smell been reduced or absent **for more than 12 weeks during the last 12 months?**

NO YES

12. Has a doctor **ever** told you that you have **chronic** sinusitis?

NO YES

12. A In the past 12 months, have you had at least one episode of at least ten days where you had a blocked nose, discoloured nasal discharge (snot) **and** pain or pressure over the sinuses?

IF 'NO' GO TO QUESTION 13

IF 'YES'GO TO QUESTION 12.A.1.

12.A.1. How many of these episodes of at least 10 days where you had a blocked nose, discoloured nasal discharge (snot) **and** pain or pressure over the sinuses did you have **in the past 12 months**?

1 2 3 4 >4

NO YES

12.A.2. Have you visited a doctor for one of these episodes?

NO YES

12.A.3. Have you received antibiotics for one of these episodes?

NO YES

12.A.4. Have you received a corticosteroid nose spray for one of these episodes?

NO YES

13. Have you ever had an itchy rash that was coming and going **for at least 6 months?** ☐ ☐

IF 'NO', GO TO QUESTION 14 ***IF 'YES' GO TO QUESTION 13.1***

NO YES

13.1 Have you had this itchy rash **in the last 12 months**? ☐ ☐

NO YES

13.2 Does this affect **only** your hands? ☐ ☐

NO YES

14. Have you ever had eczema or any kind of skin allergy? ☐ ☐

NO YES

15. Have you ever had any difficulty with your breathing within 3 hours after taking a pain killer? ☐ ☐

IF 'NO' GO TO QUESTION 16 ***IF 'YES' GO TO QUESTION 15.1***

15.1 Please write the name of the tablet? .....

NO YES

16. Have you ever smoked for as long as a year? ☐ ☐

['YES' means at least one cigarette per day or one cigar per week for one year]

IF 'NO' GO TO QUESTION 17 ***IF 'YES' GO TO QUESTION 16.1***

YEARS

16.1 How old were you when you started smoking? ☐☐

NO YES

16.2 Have you smoked at all in the **last month**? ☐ ☐

IF 'YES' GO TO QUESTION 16.3 ***IF 'NO' GO TO 16.2.1***

YEARS

16.2.1 How old were you when you stopped smoking? ☐☐

Cigarettes per day

16.3 On average how much do you (or did you) smoke? ☐☐

17. Are you currently: ***Tick one box only!***

a. employed	☐	1.
b. self-employed	☐	2.
c. unemployed	☐	3.
d. not working because of poor health	☐	4.
e. full-time house person	☐	5.
f. full-time student	☐	6.
g. retired	☐	7.
h. other	☐	8.

18. Are you currently working:

	NO	YES
a. As a health care worker (e.g. as a nurse, medical technician, doctor, paramedic or similar)?	☐	☐
b. In a job that is mainly involved with any sort of cleaning?	☐	☐

	NO	YES
19.1 Do you understand the language in which this questionnaire is composed?	☐	☐

19.2 Which language do you speak most when you're at home? ☐

19.3 Which language do you speak most when you're away from home? ☐

20.1 In which country were you born? ☐

20.2 In which country was your father born? ☐

20.3 In which country was your mother born? ☐

Tick one box only!

20.4 What is your ethnicity?

a. Caucasian/white	☐ 1.
b. Asian	☐ 2.
c. African/Creole	☐ 3.
d. Latin-American	☐ 4.
e. Hindustani	☐ 5.
f. Mediterranean	☐ 6.
g. Other (please specify):	☐

20.5 How many years have you been living in The Netherlands? YEARS ☐☐

21. What is your date of birth? DAY ☐☐ MONTH ☐☐ YEAR **19**☐☐

22. What is today's date? DAY ☐☐ MONTH ☐☐ YEAR **20**☐☐

23. Are you male or female? MALE ☐ FEMALE ☐

24. What is your postal code? ☐☐☐☐ ☐☐

May we contact you again for further scientific research? NO ☐ YES ☐

Chapter 2.2

Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis – a GA²LEN study

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Abstract

Background

The European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) incorporates symptomatic, endoscopic, and radiologic criteria in the clinical diagnosis of chronic rhinosinusitis (CRS), while in epidemiological studies, the definition is based on symptoms only. We aimed to assess the reliability and validity of a symptom-based definition of CRS using data from the GA^{2}LEN European survey.

Methods

On two separate occasions, 1700 subjects from 11 centers provided information on symptoms of CRS, allergic rhinitis, and asthma. CRS was defined by the epidemiological EP3OS symptom criteria. The difference in prevalence of CRS between two study points, the standardized absolute repeatability, and the chance corrected repeatability (kappa) were determined. In two centers, 342 participants underwent nasal endoscopy. The association of symptom-based CRS with endoscopy and self-reported doctor-diagnosed CRS was assessed.

Results

There was a decrease in prevalence of CRS between the two study phases, and this was consistent across all centers (-3.0%, 95% CI: -5.0 to -1.0%, $I^2 = 0$). There was fair to moderate agreement between the two occasions (kappa = 39.6). Symptom-based CRS was significantly associated with positive endoscopy in nonallergic subjects, and with self-reported doctor-diagnosed CRS in all subjects, irrespective of the presence of allergic rhinitis.

Conclusion

Our findings suggest that a symptom-based definition of CRS, according to the epidemiological part of the EP3OS criteria, has a moderate reliability over time, is stable between study centers, is not influenced by the presence of allergic rhinitis, and is suitable for the assessment of geographic variation in prevalence of CRS.

Introduction

Chronic rhinosinusitis (CRS), a disease defined as chronic inflammation of the nose and paranasal sinuses, has a considerable impact on morbidity and quality of life. There are varying estimates of disease prevalence based on a limited amount of data [1-4], and to date, no pan-European epidemiological study has been undertaken. The paucity of comparable and reliable data is in part related to the lack of uniformly accepted diagnostic criteria for CRS. Although a number of guidelines and consensus documents have been developed, considerable differences in diagnostic criteria and the lack of an accepted gold standard diagnosis make it difficult to make comparisons.

Upper airway diseases present with a variable pattern of common symptoms such as nasal obstruction and discharge, making the epidemiological diagnosis of CRS difficult to differentiate from allergic and nonallergic rhinitis based on symptomatic grounds only. Moreover, not all patients presenting with symptoms meeting CRS criteria have evidence of disease if diagnosis is complemented with nasal endoscopy and CT. The 2007 EP3OS guideline [5] incorporates symptomatic, endoscopic, and radiologic criteria in the clinical diagnosis of CRS. However, as nasal endoscopy and CT are difficult to apply in large-scale epidemiological studies, the EP3OS document defines CRS by symptoms only, when used in epidemiological studies. The repeatability and the validity of the EP3OS criteria have not yet been validated extensively.

Recently, the Global Allergy and Asthma European Network of Excellence (GA^{2}LEN) initiated a large epidemiological study comprising a postal survey (the GA^{2}LEN Survey) followed by a case–control study (the GA^{2}LEN Survey Follow-Up), on allergy, asthma, and upper airway disease across Europe. In this study, diagnosis of CRS is based on a questionnaire for symptoms forming part of the EP3OS diagnostic criteria. The current study aims to validate this by reporting the repeatability of the epidemiological EP3OS symptom criteria, and by describing the relationship of symptom criteria and self-reported doctor-diagnosed CRS with findings from nasal endoscopy.

Methods

Study design

In a first cross-sectional phase (the GA^{2}LEN Survey), 11 participating centers sent a questionnaire by mail to a random sample of at least 3000 subjects aged 15–75 years, with up to three attempts to elicit a response. Samples were identified by random sampling from a population-based local sampling frame.

The questionnaire was newly developed for the diagnosis of CRS (**Table 1**). A positive diagnosis of CRS was based on symptoms as defined in the 2007 EP3OS epidemiological criteria (**Table 1**); additionally, subjects were asked if a doctor had ever told whether the subject had CRS (further referred to as 'self-reported doctor-diagnosed CRS'). Asthma was defined as reporting 'having ever had asthma' and at least one of the following symptoms in the last 12 months: (i) wheeze or whistling in the chest; or (ii) waking up with chest tightness, shortness of breath or an attack of coughing. Allergic rhinitis was defined by the self-reported history of 'nasal allergy'.

In a second phase (the GA^{2}LEN Survey Follow-Up), each center invited 120 randomly selected subjects with asthma, 120 with CRS, 40 with asthma and CRS, and 120 with neither asthma or CRS for a clinical study visit with further investigations among which a questionnaire including the same questions as those described earlier for the postal survey.

Table 1. Instruments used in the GA^{2}LEN Survey and Survey Follow-up: EP3OS criteria for the diagnosis of chronic rhinosinusitis (CRS) and excerpts from the questionnaire

EP3OS criteria for diagnosis of CRS
o Presence of two or more of the following symptoms » Nasal blockage, obstruction or congestion » Nasal discharge (either anterior or posterior nasal drip) » Facial pain or pressure » Reduction or loss of smell One of which should be blockage or discharge Symptoms should be present during > 12 weeks without complete resolution
AND EITHER:
o Endoscopic signs of » Polyps, and /or » Mucopurulent discharge, primarily from middle meatus, and/ or » Edema or obstruction primarily in middle meatus
o CT changes: mucosal changes within the ostiomeatal complex and / or sinuses
Survey questionnaire
For assessing CRS as per EP3OS
o Has your nose been blocked for more than 12 weeks during the last 12 months?
o Have you had pain or pressure around the forehead, nose or eyes for more than 12 weeks during the last 12 months?
o Have you had discoloured nasal discharge or discoloured mucus in the throat for more than 12 weeks during the last 12 months?
o Has your sense of smell been reduced or absent for more than 12 weeks during the last 12 months?
Additional
o Has a doctor ever told you that you have chronic sinusitis or nasal polyps?
o Do you have any nasal allergies, including hay fever?

Nasal endoscopy

In two centers (Ghent and Amsterdam), each participant in the follow-up phase was invited to undergo nasal endoscopy. Nasal endoscopy was performed, blinded to symptom status, by otorhinolaryngology specialists or residents using routine clinical rigid 30° endoscopes. An endoscopy positive for rhinosinusitis was defined, based on the EP3OS criteria, as presence of polyps, presence of edema in the middle meatus, or presence of thick purulent discharge in the middle meatus, at either nasal side.

Statistical methods

All data available to the coordinating center that had undergone full quality control by November 1st 2009 were included in this analysis. The prevalences of CRS, each of the symptoms of CRS, asthma and allergic rhinitis in the survey and follow-up were estimated using data only from participants who had taken part in both. As the sample in the follow-up phase was selected based on disease in the survey sample (and therefore had higher prevalences of asthma, CRS and both compared to the general population), prevalence estimates were standardized, for both CRS and asthma, to the original sampled population by using inverse sampling probability weights. The standardized difference in prevalence of disease between the two phases was estimated for each center and as an overall estimate [6]. Variation of this difference between centers was estimated (Wald chi-square test for heterogeneity), and the I-squared heterogeneity measure was computed [7]. Absolute repeatability [8], standardized to account for the high prevalence of asthma, CRS and both in the follow-up phase, and Cohen's kappa (κ) statistics were derived, with confidence intervals calculated using the delta method with the normalizing transformation log (1-κ).

The odds ratios of having CRS symptoms by endoscopy results or by self-reported doctor-diagnosed CRS were derived and tested with Pearson chi-square test. To assess whether these associations were similar in subjects with and without current allergic rhinitis (defined as self-reported nasal allergy or hay fever, plus sneezing, runny or blocked nose in the absence of a cold in the last 12 months), analyses were stratified by current allergic rhinitis, the Breslow-Day test was used to test for interaction, and the Mantel–Haenszel weighted odds ratio was calculated. Binomial confidence intervals according to Clopper and Pearson were calculated around proportions. All statistical analyses were carried out using stata Version 11 (StataCorp, College Station, TX, USA) and SPSS Version 15 (SPSS Inc., Chicago, IL, USA).

Results

Eleven centers in seven countries provided data from baseline and follow-up surveys to the coordinating center by November 2009. One center which had not yet completed the study was excluded. A total of 36 790 subjects had completed the postal questionnaire, and 1700 subjects had been seen in the follow-up clinical visit. In this group, 652 were controls, 469 had asthma but no sinusitis, 411 had sinusitis but no asthma, 168 had asthma and sinusitis. Of these, 50.1% were women, the median age was 48.7 years (IQR 36.8–59.6 years), and the median time between postal survey and clinical visits was 287 days (IQR 205–359 days).

Results are based on the subjects who had taken part in both phases of the study (n = 1700). **Table 2** shows the standardized difference in prevalence between the two study phases, the absolute repeatability (standardized for disease prevalence), and the unstandardized kappa statistic, for CRS, asthma, allergic rhinitis, and some of their related symptoms. **Figure 1** illustrates the standardized difference in prevalence between the two study phases for the outcomes CRS, asthma, and allergic rhinitis in each of the participating centers.

The prevalence of symptom-based CRS, estimated from the second phase, was lower than that obtained in the first phase (-3.0%; 95% CI -5.0 to -1.0%), and this difference was similar in all centers ($I^2 = 0$). Standardized absolute repeatability of symptom-based CRS was 91.8%, and the unstandardized kappa was 39.6. All of the individually reported symptoms that contributed to the symptom-based definition of CRS showed a pattern similar to that of CRS.

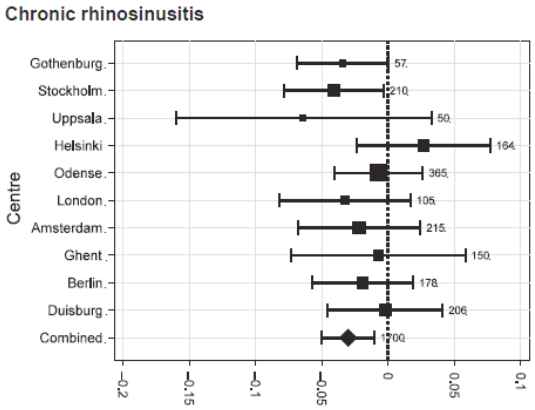
The prevalence of self-reported doctor-diagnosed CRS was lower than symptom-based CRS, with a marginally higher kappa (48.8). The standardized difference in prevalence showed an overall increase in prevalence in the second phase, with significant heterogeneity between centers ($I^2 = 52.0$; $P = 0.028$). By comparison, the prevalence of wheezing with breathlessness showed a nonsignificant ($P = 0.18$) fall between the two study phases with significant variation between centers ($I^2 = 58.9$; $P = 0.0095$). The unstandardized kappa (54.6) showed a moderate agreement.

The prevalence of asthma showed no significant standardized difference between the baseline and clinical follow-up, with nonsignificant variation of this between centers ($I^2 = 41.5$; $P = 0.082$).

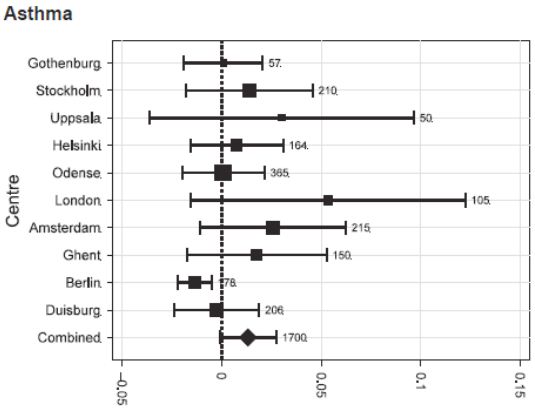
The reporting of a history of 'hay fever or nasal allergies' showed no significant difference in prevalence between the two study phases, a standardized repeatability similar to that for CRS, and an unstandardized kappa (72.8) indicating good agreement.

Table 2 Standardized change in prevalence between survey and follow-up, standardized absolute repeatability, and unstandardized kappa, for questionnaire items and for symptom-defined chronic rhinosinusitis (CRS) and asthma. Between-center heterogeneity is expressed as I^2.
SOB = shortness of breath

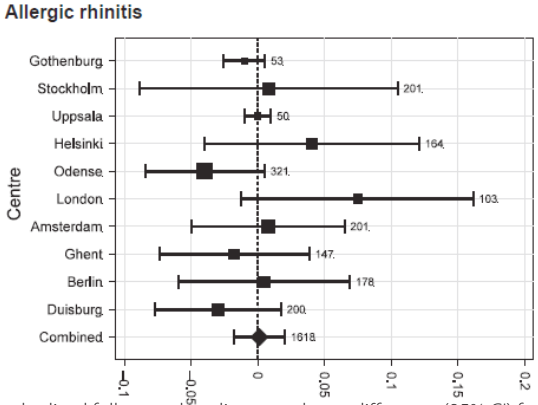
			Standardized difference in prevalence						
						Tests for heterogeneity			
Outcome	**N**	**Standardized prevalence in postal survey (%)**	**Diff (%)**	**95% CI**	**p**	**I^2**	**p**	**Absolute repeatability**	**Kappa**
CRS	1700	9.3	-3.0	-5.0 to -1.0	0.003	0.0	0.570	91.8	39.6
Blocked nose	1687	13.3	1.3	-4.8 to 7.3	0.680	52.5	0.026	84.7	45.4
Pain or pressure	1691	7.2	-3.1	-5.0 to -1.2	0.002	50.5	0.034	93.0	35.7
Discoloured nasal discharge	1687	6.8	-1.5	-2.7 to -0.3	0.012	45.6	0.057	93.3	33.5
Reduced sense of smell	1683	6.9	-1.0	-1.9 to -0.1	0.034	55.3	0.018	95.4	53.0
Doctor-diagnosed CRS	1685	2.9	5.7	0.2 to 11.2	0.040	52.0	0.028	92.3	48.8
Asthma	1700	8.0	1.3	-0.1 to 2.7	0.066	41.5	0.082	96.5	82.3
Wheezing with SOB	1602	13.3	-3.8	-9.3 to 1.8	0.180	58.9	0.001	89.6	54.6
Nasal allergy	1618	41.8	0.1	-1.8 to 2.0	0.900	8.5	0.360	92.0	72.8



Standardized follow up-baseline prevalence difference (95% CI) for: Chronic sinusitis



Standardized follow up-baseline prevalence difference (95% CI) for: Asthma



Standardized follow up-baseline prevalence difference (95% CI) for: nasal allergies

Figure 1. Standardized difference in prevalence between survey and follow-up for each center (squares) and for the whole sample (diamonds), for chronic rhinosinusitis, asthma, and allergic rhinitis.

Association of symptoms with endoscopy and self-reported doctor-diagnosed CRS

Three hundred and forty-two participants in Ghent and Amsterdam underwent nasal endoscopy. **Table 3** shows the associations of symptom-based CRS with endoscopy and selfreported doctor-diagnosed CRS, stratified for current allergic rhinitis. Overall, 61.7% (95% CI: 50.3–72.3%) of symptom-positive subjects had a positive endoscopy, and 38.0% (32.3–44.1%) of symptom-negative subjects had a positive endoscopy. Of positive endoscopies, 33.6% (26.0–41.7%) had CRS symptoms, and 83.9% (77.9–88.8) of negative endoscopies had no CRS symptoms. A total of 31.4% (21.8–42.3) of symptom-positive and 11.1% (7.7–15.4%) of symptom-negative subjects had a self-reported doctor-diagnosed CRS. Symptom-based CRS was significantly associated with a positive endoscopy (OR 2.62; 95%CI [1.57–4.39]; $P < 0.001$) and with middle meatal purulent secretions and middle meatal edema. The association of symptom-based CRS to a positive endoscopy was stronger in subjects without current allergic rhinitis (OR 3.78; $P < 0.001$) compared to subjects with allergic rhinitis (OR 1.45; $P = 0.437$), and the Mantel–Haenszel corrected OR was comparable with the uncorrected OR (OR 2.41 [1.43–4.05], $P < 0.001$) (**Table 3**). The Breslow-Day test showed no significant differences between odds ratios of each subgroup. Symptom-based CRS was associated with a selfreported doctor-diagnosed CRS (OR 3.67 [2.03–6.60], $P < 0.001$). This association was not modified by the presence of allergy (adjusted OR 3.62 [1.97–6.63], Breslow-Day $P = 0.871$).

Table 3. Associations of symptom-based chronic rhinosinusitis (CRS) with endoscopy and self-reported doctor-diagnosed CRS, stratified for current allergic rhinitis (n = 342). Interaction effects were tested with Breslow-Day's test. AR = allergic rhinitis

	Crude Odds ratio			Subjects without current AR		Subjects with current AR		Breslow-Day test	Mantel-Haenszel adjusted odds ratio		
	OR	95% CI	P (χ^2)	OR	95% CI	OR	95% CI	P	Adj. OR	95% CI	P
Middle meatal findings											
Purulent secretions	3.36	1.55-7.31	0.003	4.30	1.58-11.7	2.33	0.67-8.17	0.454	3.29	1.49-7.25	0.003
Edema	2.63	1.58-4.37	<0.001	3.67	1.81-7.45	1.46	0.68-3.12	0.080	2.36	1.41-3.94	0.001
Positive endoscopy	2.62	1.57-4.38	<0.001	3.78	1.84-7.75	1.45	0.67-3.13	0.074	2.41	1.43-4.05	0.001
Doctor-diagnosed CRS	3.66	2.03-6.60	<0.001	3.79	1.71-8.43	3.43	1.37-8.60	0.871	3.62	1.97-6.63	<0.001

Discussion

The revised EP3OS consensus document provided diagnostic criteria for CRS in 2007, and we have applied these criteria in a two phase, multicenter, questionnaire-based cross-sectional epidemiological study, the GA^{2}LEN Survey and the GA^{2}LEN Survey Follow-Up. Endoscopic findings, characteristic of CRS (as defined by the EP3OS criteria), and the reporting of doctor-diagnosed CRS was used to assess the validity of the reported symptoms for defining CRS in this setting.

We used three parameters to assess the reliability of the CRS questionnaire: standardized difference in prevalence, standardized absolute repeatability, and unstandardized kappa statistic. When using general population surveys to describe between center differences in chronic disease prevalence, a prevalence estimate that is stable over time is needed, even though individual changes (disease incidence and disease remission) may be occurring within the population. The absence of change in prevalence implies that, at population level, the number of subjects who are asymptomatic in the first phase but have symptoms in the second phase is equivalent to the number of those with symptoms in the first phase who report no symptoms in the second phase. We observed a decrease in prevalence of CRS between the two occasions. We also observed a decrease in prevalence for 'wheezing with breathlessness', a commonly used symptom question in respiratory epidemiology. The magnitude of the difference for CRS was equivalent to that seen for 'wheezing with breathlessness' and most importantly showed no variation between centers. This means that there is no evidence that the broad interpretation of geographic variation in prevalence of disease using this instrument will be affected (that is, the error is constant across populations).

Absolute repeatability was high for all questions, and to some extent this is not surprising as within subject agreement for low prevalence conditions is likely to be solely because of the chance.

Unstandardized repeatability (Cohen's κ) was fair to moderate for CRS questions and for symptom-based CRS definition, whereas it was moderate to good for asthma and nasal allergy. Cohen's kappa is a widely accepted measure to assess chance-corrected agreement [9] but it has been argued that in questionnaire development for assessing symptoms in population-based studies (where the prevalence of the out-come is low) survey items should not be rejected on the basis of kappa alone [8]. Other parameters should be considered, including change in prevalence and measures of validity against clinical criteria.

Development of instruments suitable for the epidemiological investigation into CRS is hampered by the lack of an easily measurable gold standard definition of

disease. We compared symptom criteria to endoscopy and to self-reported doctor-diagnosed CRS, which are assumed to be highly specific, but not sensitive, for CRS. We demonstrated significant associations of the symptom criteria with positive endoscopy and doctor-diagnosed CRS. Of subjects who had positive symptoms, 62% had a positive endoscopy, whereas 38% of symptom-negative patients had a positive endoscopy. As patients in this study were required to have chronic symptoms in the last 12 months but not necessarily at the time of endoscopy, we expect that a small proportion of endoscopy-negative patients may have had a positive endoscopy during active symptoms and vice versa. To our knowledge, this study is the first to document endoscopy in asymptomatic subjects.

In line with work of Stankiewicz [10] investigating CT and endoscopy in CRS patients, we observe that only a proportion of symptom-positive patients had a positive endoscopy. However, in that study, only 29% of participants had a positive endoscopy, while 62% of our symptom-positive subjects had a positive endoscopy. This difference could be explained by less strict symptom criteria, and the exclusion of nasal polyp patients and patients with purulence on rhinoscopy. In a large hospital-based study in Istanbul, Tahamiler et al. [11] report that in 768 patients with CRS fulfilling the EP3OSsymptom criteria, 31.3% of allergic patients and 24.7% of nonallergic patients had a positive nasal endoscopy. This is a much smaller proportion than in our study (respectively 58% and 65%), but the reason for the difference is unclear, as this study used even less strict criteria for positivity of endoscopy.

In the diagnosis of CRS, controversy exists whether or not to corroborate positive symptoms with endoscopy and CT [12]. The EP3OS criteria propose a confirmation by either CT or endoscopy. As it is not possible to include CT in epidemiological studies involving healthy subjects, we can only hypothesize that some of our participants with positive symptoms but negative endoscopy may have had radiographic evidence of disease. In fact, in a study comparing CT and endoscopy using a proprietary scoring system in CRS patients [13], 65% of endoscopy-negative patients had radiographic evidence of disease. In another study [10], this proportion was 36%. Extrapolating these data to our population, we can estimate that 76–87% of our symptom-based CRS diagnoses would be confirmed by endoscopy or CT had both been available.

The study by Tahamiler suggests that the association of symptom-based CRS with objective markers of disease is not greatly influenced by the presence of allergic rhinitis. However, there is overlap in the symptoms associated with each condition, particularly for nasal obstruction and rhinorrhea [14-16]. Therefore, we might expect a weaker association of symptom-based CRS with objective markers of disease in

subjects with allergic rhinitis. We addressed this question by stratifying our analyses for current allergic rhinitis. The strength of the association of a positive endoscopy with CRS symptoms was weaker in the presence of allergic rhinitis, although we found no statistically significant evidence for this (Breslow-Day test for interaction, P = 0.074). However, it has been shown that the statistical power for testing interaction is too low in many epidemiological studies [17]. Although our observations could be explained by an overlap of CRS and allergic rhinitis symptoms, endoscopic findings such as edema can also be present in both diseases. This may account for a high proportion (49.3%) of positive endoscopies in CRS-negative allergic rhinitis patients. In contrast to endoscopy, symptom-based CRS was associated with self-reported doctor-diagnosed CRS, irrespective of the presence of allergic rhinitis.

Taken together, these findings suggest that a symptom-based definition of CRS is stable, irrespective of the presence of allergic rhinitis, and that positivity of the endoscopic criteria may be influenced by the presence of allergic rhinitis. Further research on the specificity of symptom criteria and endoscopy in relation to radiologic changes is warranted.

Conclusion

We have for the first time assessed the reliability of the symptom-based EP3OS definition for epidemiological diagnosis of CRS. Our findings suggest that a symptom-based definition of CRS has a moderate reliability over time, is stable between study centers, is not influenced by the presence of allergic rhinitis, and is suitable for the epidemiological assessment of geographic variation in prevalence of CRS.

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Chapter 3

Rhinosinusitis in primary care

Chapter 3.1

Rhinosinusitis in morbidity registrations in Dutch general practice: a retrospective case control study

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Abstract

Background

There is only limited accurate data on the epidemiology of rhinosinusitis in primary care.

Aims

To assess the incidence of acute and chronic rhinosinusitis by analysing data from two Dutch general practice registration projects. Several patient characteristics and diseases are related to the diagnosis rhinosinusitis.

Methods

The Continuous Morbidity Registration (CMR) and the Transitionproject (TP) are used to analyse the data on rhinosinusitis in primary practice. Both registries use codes to register diagnoses.

Results

In the CMR 3244 patients are registered with rhinosinusitis and in the TP 5424.

CMR : The absolute incidence of (acute) rhinosinusitis is 5191 (18.8 per 1000 patient years). Regarding an odds ratio of 5.58, having nasal polyps is strongest related to rhinosinusitis compared to the other evaluated comorbidities. A separate code for chronic rhinosinusitis exists, but is not in use.

TP: Acute and chronic rhinosinusitis are coded as one diagnosis. The incidence of rhinosinusitis is 5574 or 28.7 per 1000 patient years. Patients who visit their general practitioner with "symptoms/complaints of sinus", allergic rhinitis and "other diseases of the respiratory system" have the highest chances to be diagnosed with rhinosinusitis. Medication is prescribed in 90.6 % of the cases.

Conclusions

Rhinosinusitis is a common diagnosis in primary practice. In the used registries no difference could be made between acute and chronic rhinosinusitis, but they give insight in comorbidity and interventions taken by the GP in case of rhinosinusitis.

Background

Rhinosinusitis is one of the commonest reasons for general practice visits and can have a substantial influence on a person's quality of life [1-4]. Despite the high prevalence and significant morbidity of rhinosinusitis, there is only limited accurate data on the epidemiology of this condition. This is mainly due to the lack of an generally accepted definition for rhinosinusitis and the different patient selection criteria in epidemiological studies.

A taskforce endorsed by the European Academy of Allergology and Clinical Immonology and the European Rhinologic Society has come up with clear unambigious definitons of rhinosinusitis which can be used for epidemiological and clinical research (The European Position Paper of Rhinosinusitis and Nasal Polyps, EPOS) [5]. EPOS is the first combined guideline for primary and secondary medical care [5-7]. The EPOS definition of rhinosinusitis is defined as two or more symptoms one of which should be either nasal obstruction or nasal discharge. Other possible symptoms are facial pain/pressure or impairment of smell. In acute rhinosinusitis (ARS), this condition is present for less than 12 weeks, in chronic rhinosinusitis (CRS) for more than 12 weeks. Recurrent rhinosinusitis is defined as at least 4 episodes of rhinosinusitis within one year with complete resolution of symtoms between the episodes [5].

In Europe, CRS is an underestimated disease. Data on the prevalence of rhinosinusitis in European populations are rare. For this reason the European Union has funded a large epidemiological survey in more than 20 countries, the Global Allergy and Asthma European Network (GA^{2}LEN) survey, which provides the first European epidemiological data on the prevalence of rhinosinusitis. According to this publication, the overall prevalence of CRS by EPOS criteria was 10.9% [8]. In Portugal a study was done with cadaver specimens with a mean age of death of 77 years. The prevalence of nasal polyps was 5.5% [9].

General practitioners (GPs) play a vital role in the Dutch health care system. They are the gate-keepers to specialist care. Nearly all inhabitants are registered with a general practitioner. As most of the health problems presented to GPs are not seen by specialists, general practices are important sources of information about common diseases [10]. In a survey by the Netherlands Central Bureau for Statistics 60 per 1000 Dutch inhabitants in 1992 considered themselves to suffer/have suffered from rhinosinusitis [11].

The estimated incidence of ARS in Dutch general practices in 2003 was 16.4 per 1000 men and 33.3 per 1000 women. This means that at total of 131800 men and 273000 women were diagnosed with ARS in 2003 [12]. In the "Second National Study",

a report on diseases and interventions in general practice, an incidence of 22.1 per 1000 patients was reported. (15.2 per 1000 men and 28.8 per 1000 women) [13]. In the UK figures of 25 per 1000 patient years have been reported [11]. No differentiation was made between ARS and CRS in these last two reports.

In the current study, two Dutch general practice morbidity registrations projects were used; the Nijmegen Continuous Morbidity Registration (CMR) and the Transitionproject (TP). The aim of our study was to assess the incidence of ARS and CRS diagnosed by GPs by analysing data from these two Dutch general practice registration projects. We also looked at patient characteristics, comorbidity, reasons for consulting the GP and interventions taken by the GP.

Methods

This retrospective case-control study did not need approval of an ethical board since the anonymous participants in the already existing database were not submitted to investigations or actions as part of this study.

General practice morbidity registrations

We used the databases of the following two general practice morbidity registrations to estimate the incidence of ARS and CRS. Permission was granted to access both databases.

Nijmegen Continuous Morbidity Registration

The CMR involves four general practices in the region of Nijmegen in the Netherlands. The goal of the CMR is to generate epidemiological numbers concerning diseases in the general practice population for the purpose of education and scientific research. Since 1971 all common diseases and all referrals to specialists are entered in this registration, as are all hospital admissions [14]. Background information like date of birth, gender, socioeconomic status, date of practice entry, date and reason of leaving the practice is also registered. Socioeconomic status is divided in three social classes, which are based on the occupation of the wage earner (based on a classification of the Institute for Applied Sociology).

For the current study we used CMR data from 1985 until 2006 comprising an average population of approximately 12,000 patients and 275,602 patient years. All patients who had been diagnosed with rhinosinusitis were included in this study. In the CMR a list of codes based on the E-list (compatible with the ICHPPC-2-defined criteria (ICHPPC: International Classification of Health Problems in Primary Care)) is used (**Figure 1**). In the CMR, separate codes for ARS and CRS exist. However,

the code for CRS is not used consistently (as a result of an agreement between the participating GPs). To indicate whether a visit was for a new episode or for an already existing episode, the GPs in the CMR practices use a special code linked to the diagnosis. When the code for an already existing episode of rhinosinusitis was used, that (same) episode was not included again for calculation of the incidence of rhinosinusitis [14,15].

Transition project

The TP's goal is to develop and apply episode-oriented epidemiology in general practice by coding all diagnoses by the International Classification of primary Care (ICPC). Participating GPs register all contacts between patient and GP and all actions that result from the contact. The data from 1985 until 2002 are based on a population from three practices in the city of Amstelveen and two practices in the province of Friesland with approximately 18,000 patients and 201,137 patient years of observation. Variables that are documented in the TP are patient characteristics, reasons for encounter, interventions initiated by the GP and referrals [14]. Only the kind of intervention was coded, for example prescription of medication, but not exactly which medicament was prescribed. **Figure 1** shows the criteria for inclusion in the rubric rhinosinusitis [16].

	Code	
CMR	**2430**	• Pus obtained directly from a sinus **AND/OR** **Two of the following:** • Purulent nasal or postnasal discharge, or previous medically treated episodes of RS • Tenderness over one or more sinuses, or deep-seated aching facial pain • Radiological evidence of rhinosinusitis or opacity on transillumination

	Code	
TP	**R75**	• Purulent nasal or postnasal discharge, or • Previous medically treated episodes of RS **AND** • Tenderness over one or more sinuses, or • Deep-seated aching facial pain, or • Opacity on transillumination
		OR
		• Radiological evidence of rhinosinusitis
		OR
		• Pus obtained directly from a sinus

Figure 1. Inclusion in rubric rhinosinusitis

The code for reason for encounter could represent a complaint or the diagnosis itself. In the latter case, the patient had the suspicion of having that particular disease and reported this to the GP.

In the TP no difference is made between ARS and CRS. However, the length of the episodes of care is registered in the TP and we tried to use this information to discriminate between ARS and CRS.

Comorbidity

The commonest comorbidities or predisposing conditions for rhinosinusitis mentioned in literature [1,5,17] are: viral infections (upper respiratory tract infections), allergic rhinitis, anatomical variations of the nose, immunocompromised state, nasal polyps, asthma/COPD (chronic obstructive pulmonary disease) and dental infections. Nasal polyps may be part of the diagnosis (chronic) rhinosinusitis, but a separate code in which nasal polyps are mentioned exists in both morbidity registrations. These characteristics were included in the study and related to the diagnosis rhinosinusitis.

Statistical analysis

We analysed the data from the CMR and TP by calculation of odds ratios (odds of comorbidity in rhinosinusitis population/odds of comorbidity in population without rhinosinusitis). Statistically an odds ratio above 1.0 and a 95% confidence interval not including 0 is a significant association, but maybe not clinically relevant, therefore we considered an odds ratio of more than 3.0 in combination with the lower limit of the 95% confidence interval above 2.0 to be a relevant association.

Results

Incidence of ARS and CRS in the CMR

Based on the above mentioned criteria, a total of 3244 patients were found to be registered with one or more episodes of ARS in the CMR in the period 1985 to 2006. The incidence of ARS in the CMR was 5191, corresponding with 18.8 per 1000 patientyears. ARS incidence varied slightly over the years, with an apparent trend to lower incidence in the period 1989 to 2004. The code for incident cases of CRS was only used in 33 cases (0.1 per 1000 patientyears). The prevalence of ARS and CRS was 5197 (18.9 per 1000 patientyears) and 65 (0.2 per 1000 patientyears) respectively.

The population with rhinosinusitis in the CMR was mainly from the lowest social class (40.1%); 14.4% was from the highest social class.

The incidence of ARS was unequally distributed over the age groups and sexes. The incidence in men was 14.4, in women 23.1 per 1000 patient years (**Figure 2**). The incidence was highest in the 25-44 years age group, with 39.4 per 1000 patient years for women and 23.4 per 1000 patient years for men. There were 27 children below the age of 4 who had been diagnosed with ARS.

Incidence of ARS and CRS in the TP

Reliable determination of the length of episodes was not possible in the TP data, despite the code for the end of an episode. Because an episode can end in between two visits to the GP, the exact end of an episode remains unknown. Therefore no discrimination between ARS and CRS could be made. In the TP 5424 patients had been diagnosed with one or more episodes of rhinosinusitis in the period 1985 to 2002. The total incidence of rhinosinusitis in the TP was 5574, or 28.7 per 1000 patient years. The distribution of rhinosinusitis over the age groups and sexes was comparable to the distribution in the CMR (**Figure 2**). The incidence in men was 21.3 per 1000 patient years, in women 35.6 per 1000 patient years. Again, the incidence was highest in the 25-44 years age group. The incidence of rhinosinusitis in women was 53.3 per 1000 patient years and in men 29.3 per 1000 patient years. In the TP 100 children aged 0-4 years had been diagnosed with rhinosinusitis.

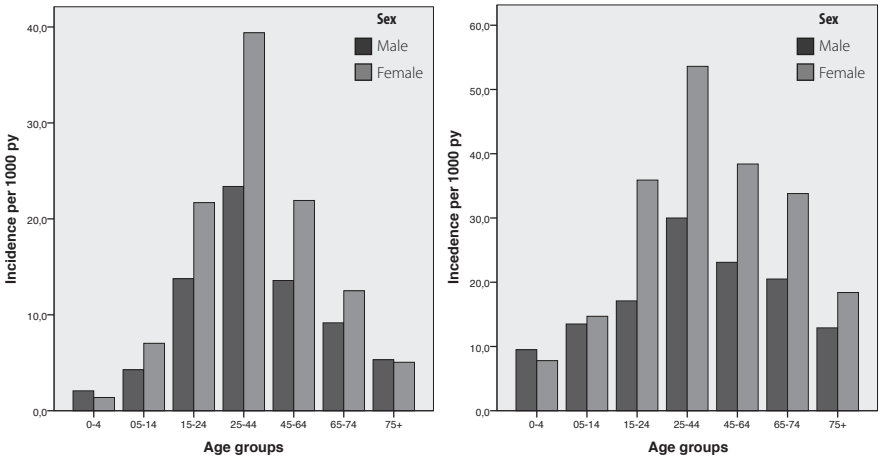

Figure 2. Incidence of acute rhinosinusitis in men and women of different age groups. CMR and TP

Number of episodes with rhinosinusitis

GPs of the CMR reported a total of 3244 patients having 5191 episodes of acute rhinosinusitis between 1985 and 2006. Most of these patients (69%) only had one episode during the period of registration, the rest had one or more relapses. Most of them (18%) had one documented relapse, one patient even had up to 22 relapses. Only four patients met the criteria for recurrent rhinosinusitis mentioned before.

In the TP database 5424 patients experienced 5774 incident cases of rhinosinusitis.

Comorbidity and rhinosinusitis

To assess whether comorbidity was related to the incidence of ARS in the CMR database, a few diagnoses were related to the diagnosis "ARS". **Table 1** compares the incidence of comorbidity in the rhinosinusitis group with the incidence of morbidity in the population without rhinosinusitis. The rhinosinusitis population represented 50,888 patient years. With an odds ratio of 5.58 and the lower limit of the 95% confidence interval being 4.46, "nasal polyps" was the only comorbid condition that was significantly associated with rhinosinusitis. With an odds ratio of 2.88 (95%CI 2.70 to 3.07), allergic rhinitis showed a tendency towards a significant association. Analysis of comorbidity from the TP also showed an association between allergic rhinitis and rhinosinusitis and between "other diseases of the respiratory system" and rhinosinusitis (**Table 2**). The other selected diseases did not meet the cut-off to confirm a significant association.

Table 1. Odds ratio of morbidity for patients with rhinosinusitis relative to controls without rhinosinusitis, CMR

Comorbidity	Odds ratio	95 % CI
Viral infection (without fever)	1.57	1.53 – 1.62
Allergic rhinitis	2.88	2.70 – 3.07
Dental infections	1.40	1.29 – 1.52
Asthma	1.46	1.38 – 1.54
Nasal polyps	5.58	4.46 – 6.97

Table 2. Odds ratio morbidity (odds morbidity in rhinosinusitis/odds morbidity non-rhinosinusitis), TP

Comorbidity	Odds ratio	95% CI
Allergic rhinitis	4.06	3.62 – 4.55
Other disease resp. system (including nasal polyps)	3.63	2.81 – 4.70
Asthma	2.30	2.03 – 2.61
Upper resp. tract infections	2.16	1.99 – 2.34
Emphysema/COPD	1.11	0.84 – 1.46
Disease of teeth/gums	1.07	0.72 – 1.58

Reason for encounter in rhinosinusitis

Analysis of the TP database showed that the commonest reason for encounter before the GP recorded rhinosinusitis as his/her diagnosis was "Symptoms/complaints sinus, including pain". Other frequent reasons for encounter were upper respiratory tract infections and headache. Children aged 0 to 4 years consulted with a cough or fever relatively often. Adolescents' (age between 15 and 24 years) top-3 reasons for encounter were cough, headache and symptoms/complaints of the sinus. Patients older than 65 usually came with symptoms/complaints of the sinus, but also relatively often with a cough (**Table 3**).

GPs' interventions for rhinosinusitis

Table 4 shows the diagnostic assessment and interventions of the GP for patients with rhinosinusitis from the TP database. GPs medically examined most patients and almost 91% received a prescription for medication to treat the rhinosinusitis. Unfortunately, no details were recorded about the precise examinations the GPs performed and the medication that was prescribed. Of all patients diagnosed with rhinosinusitis by the GPs, 7.6% was sent for diagnostic radiology.

Young children (aged 0-4 years) received less prescriptions for medication than patients in other age groups, but were referred more often than patients from other age groups (**Table 4**). Of the total population 2.7% was referred to a medical specialist. A higher percentage of children, aged between 0 and 4 was referred.

Table 3. Reason for encounter in rhinosinusitis cases (n=5774). Absolute numbers and percentage per age group. Top 10. TP

			Age group						
	Label reason for encounter	**Total N (%)**	**0-4 N (%)**	**5-14 N (%)**	**15-24 N (%)**	**25-44 N (%)**	**45-64 N (%)**	**65-74 N (%)**	**75+ N (%)**
1	Symptoms or complaints of sinus (including pain)*	2001 (24.5)	7 (4.6)	60 (11.8)	196 (21.8)	1131 (29.7)	417 (22.7)	133 (20.9)	57 (18.3)
2	Upper respiratory infection (common cold)	1000 (12.3)	16 (10.5)	60 (11.8)	126 (14.0)	464 (12.2)	243 (13.3)	54 (8.5)	37 (11.9)
3	Headache**	994 (12.2)	6 (3.9)	84 (16.5)	148 (16.4)	457 (12.0)	192 (10.5)	66 (10.4)	41 (13.2)
4	Cough	947 (11.6)	38 (24.8)	100 (19.6)	90 (10.0)	333 (8.7)	211 (11.5)	121 (19.1)	54 (17.4)
5	Sinusitis, acute or chronic***	784 (9.6)	3 (2.0)	9 (1.8)	69 (7.7)	429 (11.3)	218 (11.9)	43 (6.8)	13 (4.2)
6	Fever	386 (4.7)	35 (22.9)	60 (11.8)	31 (3.4)	141 (3.7)	70 (3.8)	30 (4.7)	19 (6.1)
7	Symptoms or complaints of throat	237 (2.9)	2 (1.3)	13 (2.5)	43 (4.8)	88 (2.3)	64 (3.5)	20 (3.1)	7 (2.3)
8	Medication/prescription/ injection	218 (2.7)	1 (0.7)	4 (0.8)	10 (1.1)	115 (3.0)	71 (3.9)	13 (2.0)	4 (1.3)
9	Sneezing/nasal congestion	211 (2.6)	4 (2.6)	17 (3.3)	36 (4.0)	81 (2.1)	37 (2.0)	26 (4.1)	10 (3.2)
10	General weakness/ tiredness	181 (2.2)	8 (5.2)	20 (3.9)	21 (2.3)	73 (1.9)	29 (1.6)	17 (2.7)	13 (4.2)

* Label "Symptoms or complaints of sinus": patients present themselves with complaints
** excluded were: N02=Tension headache, N89=Migraine, R09=Sympt/complt sinus
*** Label "Sinusitis": patients present themselves with the suspicion of having rhinosinusitis

Table 4. Percentage of rhinosinusitis cases (n=5774) with interventions. TP

			Age group						
	Label	**Total**	**0-4**	**5-14**	**15-24**	**25-44**	**45-64**	**65-74**	**75+**
1	Medical examination or health evaluation	91.3	95.0	94.0	94.2	90.5	89.5	93.2	94.0
2	Medication prescription or injection	90.6	84.0	86.3	90.4	90.0	92.4	92.7	92.1
3	Advice or health education	22.3	18.0	26.6	23.5	24.4	17.9	18.1	24.1
4	Diagnostic radiology/ imaging	7.6	9.0	9.9	7.1	7.3	8.1	6.8	6.9
5	Referral to medical specialist or hospital	2.7	9.0	2.1	2.0	2.3	3.1	3.3	4.2

Discussion

Main Findings

Although clear unambigious definitons of rhinosinusitis have been published, the diagnosis of rhinosinusitis in general practice remains complicated. Firstly the discrimination between rhinosinusitis and other upper airway diseases is difficult [5,18]. The symptomatology of rhinitis and rhinosinusitis overlap. When the patient has nasal blockage, purulent discharge and/or facial pain, it may be impossible to make an adequate diagnosis without nasal endoscopy or CT scan, none of which are usually available in the GP practice [19,20]. It was found that questionnaire-based and clinical based CRS show moderate correlation [21]. On the other hand, symptom-based CRS (based on EPOS criteria) has been shown to be significantly associated with positive endoscopy in nonallergic subjects [22].

In the two registries the GPs do not seem to differentiate between ARS and CRS, which may just be a matter of limitations of the studied registries. In a previous study from our group 69% of Dutch GPs reported to discriminate between ARS and CRS. However, their definitions of ARS and CRS varied [23].

Almost 91% of the patients with rhinosinusitis received a prescription for medication. Antibiotics are still prescribed quite often for this indication [23], even though we know that antibiotics do not influence the clinical course of sinusitis nor the rate of relapses during 1-year follow-up [24,25]. Initial management can be limited to symptomatic treatment only [26,27]. In 7.6% of the rhinosinusitis patients in our study diagnostic radiography was performed. In ARS, X-rays have no prognostic value nor therapeutical consequences [26]. In patients with clinical diagnosis of ARS it has been shown that less than half actually have significant abnormalities at X-ray examination [28].

From the data of the TP, it seems that young children are referred more easily than patients in other age groups. A likely explanation for this observation is that GPs are more cautious when they treat very young children. However, the analysis of a subgroup of only 100 children is not as reliable as the analysis on the other (larger) age groups.

Strengths and limitations of this study

It is possible that the incidence of rhinosinusitis in this study is overestimated, because the diagnosis is only based on symptoms and physical examination by the GP. For the diagnosis we depend on the GP's assessment, we are not sure that inclusion criteria are strictly followed. Based on sinus puncture/aspiration (which is considered the most accurate diagnostic test), 49-83% of a population

of symptomatic patients was proven to have ARS [29]. Furthermore, we do not know whether patients who presented with a "second" episode had complete resolution of the symptoms in between their contacts with the GP. Therefore differentiation between "recurrent" ARS and CRS is not possibible. On the other hand, incidence could be underestimated, because many patients with complaints, and possibly rhinosinusitis, do not visit their GP.

Questionnaire-based studies on rhinosinusitis exist showing a prevalence of, for example, CRS of 10.9% in Europe and even 14.3% in Amsterdam, the Netherlands [8]. This is much higher than the numbers found in current study for rhinosinusitis overall (ARS and CRS together), but it is known that questionnaire-based and clinical-based CRS show only moderate correlation [21].

Unfortunately, we could not discriminate between ARS and CRS in either of the two registries used. In the CMR, there is a separate code for chronic rhinosinusitis but the GPs from the CMR have decided not to use this code. In the TP it depends on the assessment of the GP whether a visit for an episode of rhinosinusitis following an earlier episode is considered a new episode or part of the same episode. Furthermore, it is not possible to determine the end of an episode, since the patient can recover in a period between contacts with the GP. Therefore it was impossible to determine the duration of rhinosinusitis episodes properly.

The incidence of rhinosinusitis in the TP is higher than the incidence in the CMR. Due to missing values in the TP, further statistical analysis of this difference was not possible. A possible explanation for the difference could be the fact that in the TP, the diagnosis is coded as acute/chronic rhinosinusitis. All diagnoses related to rhinosinusitis fit into this group. In the CMR, there are separate diagnose codes for ARS and CRS. The code for CRS is not used, but certain symptoms/complaints concerning the sinus do not fit into the ARS group and are probably coded otherwise. Furthermore, the criteria for inclusion in the rubric rhinosinusitis were less strict in the TP.

Not all predisposing factors could be analysed, because of their low incidence in the databases. Immunocompromised state, for example, was too uncommon to analyse. Other conditions had no separate code in the registries. Therefore these conditions could not be compared to the data of the TP. In both registries anatomical variations of the nose were not specifically coded and therefore could not be analysed. Another limitation of this study is that our results can not be easily compared to data of other studies, because it appears that this kind of analysis of GP registries has not been done before.

Ideally registries with clear inclusion criteria for rhinosinusitis, using the unambiguous definitons of rhinosinusitis as defined in EPOS, should be used in a study like this. Information on interventions should be more precise, giving more insight in the medicaments prescribed and the diagnostic radiology that is applied for.

Interpretation of findings in relation to previously published work

Okkes et al. compared data from a general population health survey of the Dutch Central Bureau for Statistics (CBS) about episodes of chronic diseases experienced by the respondents with data from general practice registration projects. The health survey resulted in higher frequencies than the GP registration for respiratory disorders, including rhinosinusitis (mostly in the age group of 25-44 years). In the CBS health survey 60 per 1000 inhabitants in the Netherlands in 1992 self-reported a diagnosis of rhinosinusitis. These numbers were compared to the numbers of three GP registries showing prevalences between 21 and 31 per 1000 patient years [11]. The differences between men and women and age groups found in this study confirm data found in the Second National Study [13]. The reason for the difference between men and women is still unclear [30]. Most of the predisposing factors for rhinosinusitis found in the literature, like nasal polyps, allergic rhinitis and other diseases of the respiratory system, were also predisposing factors in the current study [1,5,17].

In the Dutch guideline for rhinosinusitis, GPs are advised to do a medical examination only in case of long-lasting or severe complaints [30]. It is remarkable that 91.3% of the patients with an incident episode was examined by the GP. It is also remarkable to see that 90.6% of these patients got a prescription for medication. Unfortunately, we do not know which medication was prescribed. Decongestants, antibiotics, analgesics, nasal steroids and antihistamines are some of the commonly prescribed treatments, but cannot be confirmed by this study [1,5,23,30]. These numbers are comparable to the result of an observational study on acute maxillary sinusitis in France and Asia [31,32].

Implications for future research, policy and practice

The guideline on rhinosinusitis of the Dutch College of General Practitioners did not discriminate between ARS and CRS until October 2014 [30]. A considerable amount of data suggests that ARS and CRS are independent diseases with different treatments [5,33]. Therefore, a guideline discriminating between ARS and CRS would be better. Since October 2014 a new guideline for GPs has been published in which the word "acute" is added to the title "rhinosinusitis". Still there is no separate guideline for CRS [34].

To evaluate the management of rhinosinusitis of the GP in more depth, we conducted a study with additional information on e.g. medication policy [23].

Conclusions

Rhinosinusitis is a common diagnosis in general practice. Based on two morbidity registrations in general practice, the diagnosis can be related to several other diagnoses as allergic rhinitis and nasal polyps. Medication is prescribed in 91% of the cases and almost 8% is sent for diagnostic radiology.

Based on the two general practice registries and the Dutch GP guidelines, GPs do not seem to make a difference between ARS and CRS. The incidence of these two diseases could not be assessed separately. Because the different pathophysiology, diagnosis and treatment of these entities, this would deprive patients with rhinosinusitis of optimal care.

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Chapter 3.2

Management of rhinosinusitis in Dutch general practice

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Abstract

Aims

The aim was to determine whether general practitioners distinguish between the management of acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS), especially with regard to prescription of antibiotics and nasal steroids.

Methods

A questionnaire about the management of rhinosinusitis, was sent to 1000 GPs in the Netherlands.

Results

Ninety-six percent discriminated between ARS and CRS. However, the definition of ARS and CRS varied. The percentage of GPs prescribing antibiotics rose as rhinosinusitis severity increased. The prescription rate of nasal corticosteroids was highest for CRS (88.6%). Prescribing nasal corticosteroids in ARS was not very common.

Conclusions

Most GPs discriminate between ARS and CRS and 54% accepted (the EP3OS defined) 12 weeks as the division between ARS and CRS. Antibiotics and nasal steroids are commonly used agents, but the management of rhinosinusitis is not always consistent with the guidelines in place.

Introduction

Rhinosinusitis is defined as a sudden onset of two or more symptoms, one of which should be either nasal blockage or nasal discharge (anterior or posterior nasal drip). Other symptoms are facial pain or pressure, and impairment or loss of smell. When these symptoms are present for less than 12 weeks, we speak of acute rhinosinusitis (ARS). When symptoms are present for more than 12 weeks, they are considered to represent chronic rhinosinusitis (CRS). ARS can be divided in two groups: common cold/acute viral rhinosinusitis (symptoms disappear in less than 10 days) and acute non-viral/bacterial rhinosinusitis (increase of symptoms after 5 days or persistent symptoms after 10 days) [1-3].

In the Netherlands, to manage patients with rhinosinusitis, general practitioners (GPs) generally use the guideline from the Dutch College of General Practitioners [4]. This guideline does not distinguish between ARS and CRS. The treatment is based on the severity of the symptoms and the risk of developing complications. It advises treating symptoms initially. This guideline states that antibiotics are not indicated for the normal course of rhinosinusitis. Local steroids can be tried in patients with an abnormal course or recurrent complaints [4].

The European guideline, The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) advises distinguishing between ARS and CRS and basing management on the severity of the disease. Depending on severity, the recommendation for mild ARS (common cold) is to treat the symptoms, with nasal steroids being advised in moderate cases. Antibiotics are added to the treatment only when there are severe symptoms (fever >38ºC, severe pain). The treatment of first choice in the management of CRS is local steroids [1,2].

In a cross-sectional study covering 174 GPs from 89 general practices in the Netherlands, 50% of antibiotic prescriptions were found to be prescribed for respiratory disorders [5,6]. Twenty-two percent of the antibiotics for respiratory tract infections (RTIs) were prescribed for rhinosinusitis [6]. The prescription rate in sinusitis-like complaints was 67-70% [7,8]. In another study, the antibiotic prescription rate in rhinosinusitis was even 80% [9].

The prescription rates for sinus infection in the UK found in the literature were 91% and 92% [10,11]. Dutch prescription percentages for outpatient antibiotic use are relatively low compared with international figures [12-14].

It has been theorised that, by reducing the inflammatory response and mucosal swelling, a topical steroid may promote drainage and increase aeration of the sinuses, hasten the elimination of infectious organisms, and reduce the frequency

and severity of recurrences [15]. Several studies conclude that nasal steroids (in combination with antibiotics or alone) are beneficial in ARS and equally or more effective than antibiotics [15-18]. Furthermore, nasal steroids are the treatment of first choice in CRS [2,19].

Recently available data are based on general practice registries in which no distinction is made between ARS and CRS. As a result, we are not able to determine whether GPs distinguish between ARS and CRS [20].

The objective of this study was to determine whether GPs distinguish between the management of ARS and CRS and how Dutch GPs manage these two diseases (especially with regard to prescription of antibiotics and nasal steroids).

Methods

Study design

The Netherlands institute for health services research (NIVEL) was contacted for a random sample of 1000 Dutch GPs (the total GP population on 1 January 2007 was 8673 [21]). A questionnaire about management of ARS and CRS was developed by the authors of EPOS. This questionnaire was sent to the 1000 GPs. All the GPs were given an ID number to determine which GP returned the questionnaire. When GPs did not respond to the first mailing, a second questionnaire was sent 3 weeks later.

Questionnaire

The questionnaire consisted of three parts:

1. GP characteristics (kind of practice, age etc.)
2. The question of whether the GP differentiated between ARS and CRS
3. Two different questionnaires about the management of rhinosinusitis:
   a. One for GPs differentiating between ARS and CRS
   b. One for non-differentiating GPs

GPs were asked to fill out parts 1 and 2 and, depending on the answer to question 2, either part 3a or 3b.

The questionnaire consisted mainly of multiple-choice questions to facilitate participation. The questions about management of rhinosinusitis were sub-divided into questions about three categories:

- Mild rhinosinusitis: symptoms present for less than 5 days or improving thereafter

- Moderate rhinosinusitis: persistent symptoms after 10 days or worsening symptoms after 5 days
- Severe rhinosinusitis: persistent symptoms after 10 days or worsening symptoms after 5 days combined with fever > 38 ºC and/or severe pain

The GPs ranked their different treatment options from 1 to 10 (most often – least often). Since the GP scores for the different rankings of the treatment options were not normally distributed, we calculated the median rank per treatment option to describe the GPs' treatment preferences within the severity categories (questionnaire in appendix).

Analysis

The data were fed into a database and analysed with SPSS (Statistical Package for the Social Sciences) 16.0. We received information about the characteristics (sex, kind of practice, age and years of practice) of all Dutch GPs from the NIVEL to decide whether the characteristics of the GPs included in this study are representative for the entire GP population.

Results

GPs

Five hundred questionnaires were returned (a response rate of 50%). Twenty-nine GPs refused to participate, 46 GPs only completed parts 1 and 2, 395 filled out the complete questionnaire and 26 forgot to complete parts 1 and 2 but did fill out part 3a or b. Four GPs said they discriminated between ARS and CRS, but completed part 3b instead of 3a (**Figure 1**).

Four duplicate cases (IDs) were found in the responders. Since we did not know which were the right questionnaires, we used both in our analysis.

Most parameters of the GPs who returned the questionnaire (the responders) were comparable to the parameters of the GPs who did not respond (non-responders). Of the responders, 33% worked in a group practice; this figure was 60% for the non-responders (p=0.000). Furthermore, the responders worked more often alone or in a practice with one other GP than the non-responders. The only age group in which there was a significant difference between responders and non-responders was the 35-39-year group (p=0.001). Significantly more responders had worked as GPs for less than five years (**Table 1**).

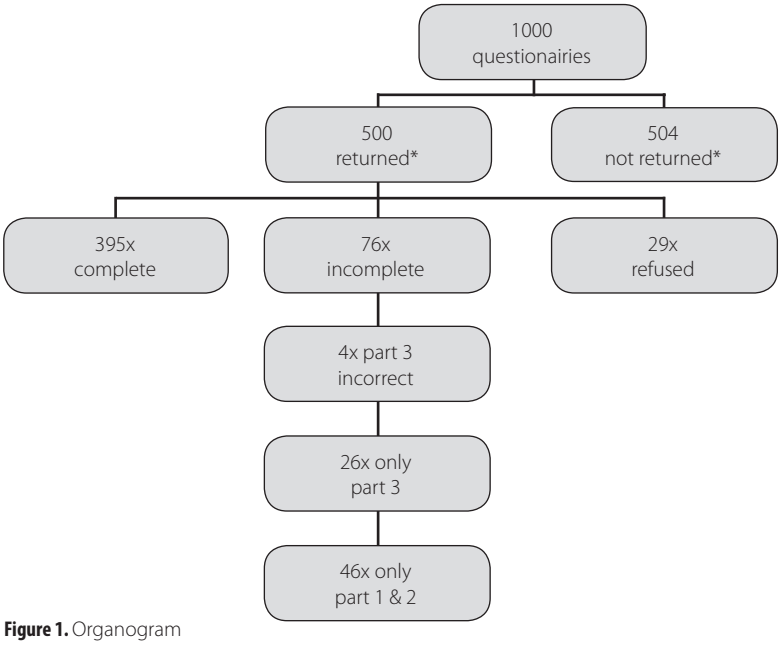

Figure 1. Organogram
* Four questionnaires were returned twice

Table 1. Characteristics

	Responders %	Non-responders %
Male	68.2	71.3
Female	31.8	28.7
Solopractice	33.9*	16.3
Duopractice	33.5*	23.5
Grouppractice	32.6*	60.2
Aged < 30 years	0.4	0.0
Aged 30-34 years	4.0	3.2
Aged 35-39 years	14.6*	8.3
Aged 40-44 years	14.4	15.4
Aged 54-49 years	16.2	14.7
Aged 50-54 years	19.8	24.1
Aged 55-59 years	19.3	22.1
Aged 60-64 years	10.8	11.0
Aged ≥ 65 years	0.4	1.3
<5 years of practice	15.5*	6.1
5-10 years of practice	17.3	19.8
10-15 years of practice	15.5	16.2
15-20 years of practice	13.1	12.8
20-25 years of practice	13.3	15.8
>25 years of practice	25.2	29.3

* Significant difference between responders and non-responders ($p<0.05$)

Do you discriminate between ARS and CRS for your treatment?

Ninety-six percent said they discriminated between ARS and CRS. The management of GPs differentiating between ARS and CRS will be further evaluated. The group of GPs that do not differentiate between ARS and CRS is too small to draw any significant conclusions.

How long must symptoms have been present before you consider a diagnosis of CRS to be appropriate?

An analysis of the answers from the differentiating group of GPs showed that most GPs see 12 weeks as the critical period (54%), with a slightly smaller group opting for 4 weeks (39%). The other 7% of the GPs adopted other periods of time (**Figure 2**).

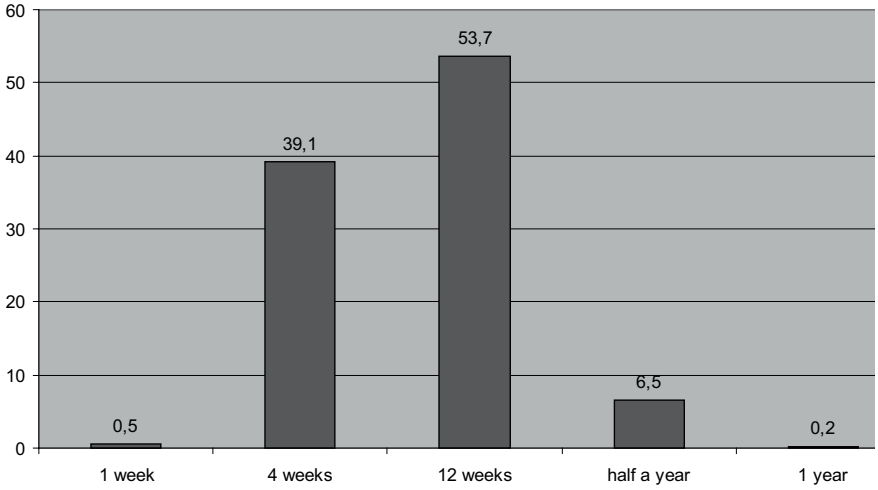

Figure 2. Duration of symptoms to consider CRS

What percentage of your population has been diagnosed with rhinosinusitis in the past 12 months?

The incidence estimate from most of the GPs in the differentiating group was 2-5% for ARS and less than 2% for CRS.

Do you agree with the following statement?
To diagnose rhinosinusitis, radiology is not recommended.

In the differentiating group, 98% of the GPs reported that there is no need for radiology in diagnosing ARS.

Opinions differed for CRS: 39% still agreed that there is no need for radiology. But 54% usually arranged an X-ray, 2% suggested a CT scan and 5% proposed something else.

Do you treat patients with mild acute rhinosinusitis?

Of the differentiating group, 51.5% treated patients with mild ARS. They prescribed decongestives most frequently (91.3%). Decongestives had a median rank of 1 (first-choice treatment). 20.6% of the GPs prescribed oral antibiotics.

However, only 2.6% of them reported that antibiotics were their first-choice treatment. The median rank for prescribing antibiotics was 4. Nasal steroids were prescribed by 19.4% of the GPs and the median rank was 3 (**Table 2**). Again, only 2.6% of them reported nasal steroids to be their first-choice treatment.

Table 2. Treatment mild ARS

	Mild ARS (%)		
No treatment	48.5		
Treatment	51.5		
	% prescribing	**Median rank§**	**% first choice**
Decongestives	91.3	1.0	61.2
Painkillers	65.8	2.0	37.2
Steaming	55.8	2.0	18.4
Nasal douche	31.7	2.0	34.9
Oral antibiotics	20.6	4.0	2.6
Nasal steroids	19.4	3.0	2.6
Oral antihistamine	6.9	4.0	0.0
Mucolytics	5.1	4.0	9.1
Systemic steroids	3.2	9.0	0.0
Other	2.8	2.5	16.7
Alternative treatment	2.3	2.0	20.0
Topical antibiotics	2.3	6.5	0.0

§ Median rank of the GPs prescribing this medicine (1=most often, 10 =least often)

Do you treat patients with moderate acute rhinosinusitis?

Most (82.5%) of the differentiating GPs treated patients with moderate rhinosinusitis. Decongestives were most frequently prescribed and were their first-choice treatment. Antibiotics were prescribed by 34% of the GPs, making them the third-choice therapy. 17.2% of the GPs prescribing antibiotics reported this treatment to be their first choice. An even higher percentage (37.3%) prescribed nasal steroids (median rank 2.5) Of these GPs, 21.7% said that nasal steroids were their preferential treatment (**Table 3**).

Table 3. Treatment moderate ARS

	Moderate ARS (%)		
No treatment	17.5		
Treatment	82.5		
	% prescribing	**Median rank§**	**% first choice**
Decongestives	83.5	1.0	59.5
Painkillers	62.3	2.0	38.7
Steaming	45.2	2.0	22.2
Nasal steroids	37.3	2.5	21.7
Oral antibiotics	34.0	3.0	17.2
Nasal douche	28.5	2.0	21.5
Oral antihistamine	7.2	4.0	0.0
Mucolytics	5.1	5.0	0.0
Systemic steroids	2.7	10.0	0.0
Alternative treatment	1.8	9.0	20.0
Topical antibiotics	1.8	9.0	16.7
Other	0.9	10.0	33.3

§ Median rank of the GPs prescribing this medicine (1=most often, 10 =least often)

Do you treat patients with severe acute rhinosinusitis?

Nearly all GPs in the differentiating group treated patients with severe ARS (99%). Antibiotics were most frequently prescribed (84%). 39.1% of the GPs prescribing antibiotics reported antibiotics to be their first choice. The median rank for prescribing antibiotics was 2, but there was no median rank 1. The most commonly prescribed antibiotic in mild, moderate and severe (A)RS was doxycycline. Nasal steroids were prescribed by 28% of the GPs treating severe ARS; 14.7% of them said nasal steroids to be their first-choice treatment. The median rank for nasal steroids was 3 (**Table 4**).

Table 4. Treatment severe ARS

	Severe ARS (%)		
No treatment	1.0		
Treatment	99.0		
	% prescribing	**Median rank§**	**% first choice**
Oral antibiotics	84.0	2.0	39.1
Decongestives	75.5	2.0	34.8
Painkillers	75.4	2.0	47.7
Steaming	40.2	3.0	15.2
Nasal steroids	28.0	3.0	14.7
Nasal douche	23	3.0	14.5
Oral antihistamine	5.1	5.0	15.0
Systemic steroids	4.8	5.0	0.0
Mucolytics	3.5	5.0	8.3
Topical antibiotics	2.3	4.5	25.0
Other	1.3	10.0	33.3
Alternative treatment	1.3	10.0	20.0

§ Median rank of the GPs prescribing this medicine (1=most often, 10 =least often)

When do you refer patients with moderate (acute) rhinosinusitis to a specialist?

Almost half of the GPs (46.5%) said that they never refer these patients to a specialist. One third reported referring after four weeks of treatment without improvement. Six percent referred after 2 weeks of treatment without improvement. One and a half percent referred after one unsuccessful course of antibiotics. The rest had other policies for referring these patients.

When do you refer patients with severe (acute) rhinosinusitis to a specialist?

One third of the GPs from the differentiating group referred after 2 weeks of treatment without result. 17.9% did this after 4 weeks and 14.2% after one course of antibiotics. Ten percent never referred and 11.4% did after 48 hours without effect of nasal steroids and/or antibiotics. Two GPs (0.5%) always referred.

When do you refer patients with ocular or neurological complications to a specialist?

Most of the differentiating GPs always referred to a specialist (87.8%). Two percent reported referring after two weeks of treatment without improvement and 3.5% after 48 hours without effect of nasal steroids and/or antibiotics.

1.7% referred after one course of antibiotics that did not work, 0.5% never referred and 4.5% did something else.

Do you treat patients with CRS?

Seventeen GPs (4.2%) did not treat these patients. Four of them always referred these patients to a specialist. The 95.8% who did treat patients with CRS prescribed nasal steroids most frequently (88.6%). Of these, 71.3% reported nasal steroids as their preferred treatment. They ranked nasal steroids first. Antibiotics were prescribed by 41.3% of the GPs, 36.9% of whom preferred this treatment above others. The median rank of antibiotics was 2 (**Table 5**).

When do you refer patients with CRS to a specialist?

Over half of the differentiating GPs (60.8%) reported referring after 4 weeks of treatment without improvement. Fifteen percent referred after 2 weeks of treatment. Two percent never referred; 1.7% always referred to a specialist and 1.2% referred after one unsuccessful course of antibiotics that did not work. The others (19.2%) had various other strategies like "on demand of the patient" or "in case of recurrence".

When do you want patients with CRS to visit you again for reassessment after you start therapy?

Most of the GPs (55.6%) wanted their patients to come back after 2 weeks and 38.7% after 4 weeks. Five GPs (1.3%) reassessed after 48 hours and 4.4% after 12 weeks.

Table 5. Treatment CRS

		CRS (%)	
No treatment		4.2	
Treatment		95.8	
	% prescribing	**Median rank§**	**% first choice**
Painkillers	47.5	2.0	28.9
Nasal steroids	88.6	1.0	71.3
Oral antibiotics	41.3	2.0	36.9
Oral antihistamine	24.5	2.0	4.5
Decongestives	22.2	2.0	22.9
Nasal douche	19.1	2.0	15.9
Steaming	14.2	3.0	14.9
Systemic steroids	9.3	3.0	16.1
Mucolytics	3.9	4.0	0.0
Other	2.1	3.5	0.0
Alternative treatment	2.1	6.5	0.0
Topical antibiotics	2.1	10.0	28.6

§ Median rank of the GPs prescribing this medicine (1=most often, 10 =least often)

Discussion

ARS and CRS may both be referred to as "rhinosinusitis", meaning "inflammation of the nose and sinuses". However, for clinical and research purposes, differentiation between these entities is preferable [2]. Although far from being completely understood, pathomechanisms in ARS and CRS are better understood today and begin to allow us to differentiate these diseases via their cytokine profile, their pattern of inflammation as well as remodeling processes [2]. It is therefore important to distinguish ARS from CRS because these two disease entities seem to have different underlying aetiologies and pathomechanisms.

Although an earlier study did not allow us to determine whether GPs differentiated between ARS and CRS [20], this study proves that they do (96% did differentiate). It is surprising that GPs do differentiate, given the guideline of the Dutch College of General Practitioners, which does not distinguish between ARS and CRS [4]. However, at present, a guideline for chronic rhinosinusitis that will make this distinction is being developed by (among others) otorhinolaryngologists and GPs [22].

In this study, the duration of symptoms after which the GPs report considering the condition to be CRS is not consistent. EPOS recommends a period of 12 weeks [2]. Approximately half the GPs surveyed said that they used 12 weeks as their criterion. The period used by the rest varied.

Almost no GPs use radiology for diagnosing ARS. This is in accordance with advice in the current guidelines [2,4]. The conclusion of a Dutch randomised controlled trial in 1997 was that, for patients with acute maxillary rhinosinusitis presenting to general practice, an initial radiographic examination is not necessary [23]. This study also concluded that antibiotic treatment (with amoxicillin) did not improve the clinical course of rhinosinusitis presenting to general practice [23]. Acute rhinosinusitis will often resolve in most patients without antibiotic treatment, even if it is bacterial in origin [23-26]. Common clinical signs and symptoms cannot identify patients with rhinosinusitis for whom treatment with antibiotics is clearly justified. Antibiotics are not justified even if a patient reports symptoms persisting for more than 7-10 days [26].

Data from Jacobs et al. demonstrate the continued evolution of bacterial resistance due to overprescribing antibiotics and highlight the need for limiting the unnecessary prescription of antimicrobials in community-acquired respiratory tract infections (RTIs) [27]. It has been shown that countries with high levels of consumption have higher rates of antibiotic resistance [13]. Although the antibiotic-prescription rate in the Netherlands is extremely low compared to most European countries and Dutch GPs do well [12-14], a considerable amount of antibiotics is still used unnecessarily. In our study, GPs consider prescribing antibiotics for mild to moderate acute rhinosinusitis, while the guidelines recommend otherwise.

The results of recent randomised controlled trials constitute a firm scientific basis for restrictive antibiotic prescription behaviour [23,25]. Initial management can be limited to symptom treatment [4,23].

The EPOS guidelines consider symptoms lasting for less than 5 days or improving thereafter to constitute a common cold and, in that case, symptomatic treatment is advisable. When symptoms worsen after 5 days or persist after 10 days, a distinction is made between moderate and severe ARS. Severe ARS is ARS with fever > 38 ^{o}C and/or severe pain. For moderate rhinosinusitis, topical steroids are advised; antibiotics and nasal steroids are advised for severe ARS [2]. These recommendations are based on some recent studies showing that additional nasal corticosteroids are as effective, or more so, than antibiotics [15-18]. This provides a welcome alternative to antibiotics without the negative consequences of microbial resistance. In the guideline of the Dutch College of General Practitioners, local corticosteroids are advised only after the failure of other treatment, in persistent or recurring complaints or in patients with an abnormal course of rhinosinusitis [4].

Corticosteroid prescription for moderate and severe ARS in our study was not very common. Only one-third of the GPs in our study considered prescribing corticosteroids in moderate or severe ARS. We would like to see a higher prescription rate for the treatment of moderate and severe ARS.

In the guidelines of the Dutch College of General Practitioners and in EPOS, immediate referral is recommended in the presence of alarming symptoms like periorbital oedema, displaced globe, double vision, ophthalmoplegia, reduced visual acuity, severe unilateral or bilateral headache, frontal swelling, signs of meningitis or focal neurological signs [2,4]. It is worrying that 12.2% of the differentiating GPs do not refer immediately. Patients still die of the complications of ARS [28].

According to the Dutch College of General Practitioners, referral should be considered when there is an abnormal course of the disease that does not respond to treatment, or does not respond sufficiently [4].

EPOS suggests considering referral when there is no improvement after 14 days of treatment in moderate ARS. In severe ARS cases, GPs should refer if there is no improvement in 48 hours [2]. In the general practices studied, only 6% of the GPs referred patients with moderate ARS in accordance with the EPOS recommendations.

In our study, more than half of the GPs apply for a plain X-ray in CRS cases. The sensitivity of plain film radiography when detecting sinus opacification is unacceptably low for the ethmoid, frontal and sphenoid sinuses compared to a CT scan [29]. Especially in chronic rhinosinusitis where mucosal thickening alone may be present, the drawback of overlapping structures makes evaluation of the osteomeatal complex, anterior ethmoid sinus, middle meatus and sphenoid sinus limited [30]. Plain X-rays are therefore not advisable for CRS.

For the treatment of CRS, EPOS advises GPs to prescribe nasal steroids, to advise nasal douching and to prescribe antihistamines if the patient is allergic [2]. In this study, in CRS, the prescribing rate for nasal steroids is rather high (88.6%). Patients with CRS are referred to a specialist, as recommended in EPOS (after 4 weeks of treatment without improvement) by 60.8% of the differentiating GPs [2]. EPOS advises the re-evaluation of CRS after 4 weeks [2] and 38.7% of the GPs report doing this.

The questionnaire in this study asks GPs what they say they do, but does not check that is really what they do. In an earlier study we studied morbidity registrations used by Dutch GPs. We found that 91% of the GPs prescribed medication, 3% referred to a specialist and 8% applied for radiology [20].

In conclusion, GPs do not seem to differentiate between ARS and CRS in the way described in EPOS. Their management of rhinosinusitis is not very consistent. It would be interesting to find out whether patients with rhinosinusitis benefit more from compliance with the EPOS guideline than when GPs make their own

decisions about the choice of treatment. We are therefore planning to conduct a randomised study to compare outcomes in patients with ARS presenting to general practice. If compliance with the EPOS guideline proves more effective in treating rhinosinusitis, changes may be required to the guideline of the Dutch College of General Practitioners.

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Appendix

Questionnaire

1. How long have you been practicing as a general practitioner?
   - ☐ < 5 years
   - ☐ 5-10 years
   - ☐ 10-15 years
   - ☐ 15-20 years
   - ☐ 20-25 years
   - ☐ ≥ 25 years

2. In what kind of practice do you work?
   - ☐ Solo practice
   - ☐ Duo practice
   - ☐ Group practice

3. In which age group are you?
   - ☐ < 30 years
   - ☐ 30-34 years
   - ☐ 35-39 years
   - ☐ 40-44 years
   - ☐ 45-49 years
   - ☐ 50-54 years
   - ☐ 55-59 years
   - ☐ 60-64 years
   - ☐ ≥65 years

4. From which duration of complaints would/do you speak of chronic rhinosinusitis?
   - ☐ 1 week
   - ☐ 4 weeks
   - ☐ 12 weeks
   - ☐ Half a year
   - ☐ 1 year

5. Do you differentiate between mild, moderate and severe complaints in your treatment of rhinosinusitis? YES ☐ NO ☐

6. Do you differentiate between acute and chronic complaints in your treatment of rhinosinusitis? YES ☐ NO ☐

IF YOU ANSWERED *QUESTION 6* WITH *YES*  **PLEASE FILL OUT THE *PINK* QUESTIONNAIRE.**

IF YOU ANSWERED *QUESTION 6* WITH *NO*  **PLEASE FILL OUT THE *YELLOW* QUESTIONNAIRE.**

YOU DO DISCRIMINATE BETWEEN ACUTE AND CHRONIC RHINOSINUSITIS (PINK)

The next questions are about acute rhinosinusitis.

1. What percentage of your total patients has had a diagnosis of acute rhinosinusitis during the past 12 months? (choose one)

   ☐ <2%

   ☐ 2-5%

   ☐ 6-10%

   ☐ 11-19%

   ☐ 20% or more

2. Do you agree with the following statement?
   For acute rhinosinusitis it is not recommended to take radiologic investigations.

   ☐ Agree

   ☐ Disagree, I usually request:

   Plain X-ray ☐, CT ☐, Echo ☐, others ☐_____(specify please)

   ☐ Disagree, as I request CT scan only, in cases of patients with additional problems such as very severe, immuno-compromised patients with signs of complications.

3. In general, do you treat acute rhinosinusitis patients with symptoms *less* than 5 days?

   YES ☐ NO ☐

If YES, then what is your typical treatment plan? (check all that apply)

If you answer "yes" more than once, please rank order each treatment (1=most often, 10=least often)

	Yes ☒	Numbering (1-10)
a. Painkillers	☐	____
b. Antibiotics	☐	____

(penicillin / amoxicillin-clavulanate / broad spectrum antibiotics)

Please specify the name, dosage and duration of antibiotics you have commonly used:

_____

	Yes ☒	Numbering (1-10)
c. Topical antibiotics	☐	____
d. Systemic steroids	☐	____
e. Nasal steroids	☐	____
f. Oral antihistamine	☐	____
g. Decongestants	☐	____
h. Nasal douche	☐	____
i. Steaming	☐	____
j. Mucolytics	☐	____
k. Herbal medicine	☐	____
l. Others (specify) _____	☐	____

4. In general, do you treat patients with acute rhinosinusitis with moderate symptoms (no fever, no severe pain) which persist for *more* than 5 days? YES ☐ NO ☐

If YES, then what is your typical treatment plan? (check all that apply)

If you answer "yes" more than once, please rank order each treatment (1=most often, 10=least often)

	Yes ☒	Numbering (1-10)
a. Painkillers	☐	____
b. Antibiotics	☐	____

(penicillin / amoxicillin-clavulanate / broad spectrum antibiotics)

Please specify the name, dosage and duration of antibiotics you have commonly used:

_____

	Yes ☒	Numbering (1-10)
c. Topical antibiotics	☐	____
d. Systemic steroids	☐	____
e. Nasal steroids	☐	____
f. Oral antihistamine	☐	____
g. Decongestants	☐	____
h. Nasal douche	☐	____
i. Steaming	☐	____
j. Mucolytics	☐	____
k. Herbal medicine	☐	____
l. Others (specify) _____	☐	____

5. In general, do you treat patients with acute rhinosinusitis with severe symptoms (with fever >38°C or severe pain)? YES ☐ NO ☐

If YES, then what is your typical treatment plan? (check all that apply)

If you answer "yes" more than once, please rank order each treatment (1=most often, 10=least often)

	Yes ☒	Numbering (1-10)
a. Painkillers	☐	____
b. Antibiotics	☐	____

(penicillin / amoxicillin-clavulanate / broad spectrum antibiotics)

Please specify the name, dosage and duration of antibiotics you have commonly used:

_____

	Yes ☒	Numbering (1-10)
c. Topical antibiotics	☐	____
d. Systemic steroids	☐	____
e. Nasal steroids	☐	____
f. Oral antihistamine	☐	____
g. Decongestants	☐	____
h. Nasal douche	☐	____
i. Steaming	☐	____
j. Mucolytics	☐	____
k. Herbal medicine	☐	____
l. Others (specify) _____	☐	____

6. What criteria do you typically use for referring each of the following types of acute rhinosinusitis patients to an ENT specialist?

   a. Patients with moderate symptoms (choose one)
      - ☐ Always refer them to a specialist right after diagnosis
      - ☐ When no improvement occurs after 14 days of treatment
      - ☐ When no improvement occurs after 4 weeks of treatment
      - ☐ After one course of antibiotic treatment which did not work
      - ☐ After 48 hours with no effect of intranasal corticosteroids and/or antibiotics
      - ☐ Never refer them to a specialist
      - ☐ Other (specify):_____

   b. Patients with severe symptoms (fever,pain) (choose one)
      - ☐ Always refer them to a specialist right after diagnosis
      - ☐ When no improvement occurs after 14 days of treatment
      - ☐ When no improvement occurs after 4 weeks of treatment
      - ☐ After one course of antibiotic treatment which did not work
      - ☐ After 48 hours with no effect of intranasal corticosteroids and/or antibiotics
      - ☐ Never refer them to a specialist
      - ☐ Other (specify):_____

c. Patients with ocular or neurological complications (choose one)

- ☐ Always refer them to a specialist right after diagnosis
- ☐ When no improvement occurs after 14 days of treatment
- ☐ When no improvement occurs after 4 weeks of treatment
- ☐ After one course of antibiotic treatment which did not work
- ☐ After 48 hours with no effect of intranasal corticosteroids and/or antibiotics
- ☐ Never refer them to a specialist
- ☐ Other (specify):_____

The next questions are about chronic rhinosinusitis.

7. What percentage of your total patients has had a diagnosis of chronic rhinosinusitis during the past 12 months? (choose one)

- ☐ <2%
- ☐ 2-5%
- ☐ 6-10%
- ☐ 11-19%
- ☐ 20% or more

8. Do you agree with the following statement?
   For chronic rhinosinusitis it is not recommended to take radiologic investigations.

- ☐ Agree
- ☐ Disagree, I usually request:

  Plain X-ray ☐, CT ☐, Echo ☐, others ☐_____(specify please)

- ☐ Disagree, as I request CT scan only, in cases of patients with additional problems such as very severe, immuno-compromised patients with signs of complications.

9. In general, do you treat patients with chronic rhinosinusitis?

YES ☐ NO ☐

If YES, then what is your typical treatment plan? (check all that apply)

If you answer "yes" more than once, please rank order each treatment (1=most often, 10=least often)

	Yes ☒	Numbering (1-10)
a. Painkillers	☐	____
b. Antibiotics	☐	____

(penicillin / amoxicillin-clavulanate / broad spectrum antibiotics)

Please specify the name, dosage and duration of antibiotics you have commonly used:

_____

	Yes ☒	Numbering (1-10)
c. Topical antibiotics	☐	____
d. Systemic steroids	☐	____
e. Nasal steroids	☐	____
f. Oral antihistamine	☐	____
g. Decongestants	☐	____
h. Nasal douche	☐	____
i. Steaming	☐	____
j. Mucolytics	☐	____
k. Herbal medicine	☐	____
l. Others (specify) _____	☐	____

10. After which duration of treatment do you reassess the complaints of a patient with chronic rhinosinusitits?

- ☐ After 48 hours
- ☐ After 14 days
- ☐ After 4 weeks
- ☐ After 12 weeks

11. What criteria do you typically use for referring chronic rhinosinusitis patients to an ENT specialist?

- ☐ Always refer them to a specialist right after diagnosis
- ☐ When no improvement occurs after 14 days of treatment
- ☐ When no improvement occurs after 4 weeks of treatment
- ☐ After one course of antibiotic treatment which did not work
- ☐ After 48 hours with no effect of intranasal corticosteroids and/or antibiotics
- ☐ Never refer them to a specialist
- ☐ Other (specify):_____

12. Can we call you for an interview by telephone with 3 cases. This will take approximately 20 minutes. **YES** ☐ **NO** ☐

Telephone: _____

Thank you very much for your cooperation in this survey!

YOU NOT DISCRIMINATE BETWEEN ACUTE AND CHRONIC RHINOSINUSITIS (YELLOW)

1. What percentage of your total patients has had a diagnosis of rhinosinusitis during the past 12 months? (choose one)

   ☐ <2%

   ☐ 2-5%

   ☐ 6-10%

   ☐ 11-19%

   ☐ 20% or more

2. Do you agree with the following statement?
   For rhinosinusitis it is not recommended to take radiologic investigations.

   ☐ Agree

   ☐ Disagree, I usually request:

   Plain X-ray ☐, CT ☐, Echo ☐, others ☐_____(specify please)

   ☐ Disagree, as I request CT scan only, in cases of patients with additional problems such as very severe, immuno-compromised patients with signs of complications.

3. In general, do you treat patients with rhinosinusitis with symptoms for *less* than 5 days? YES ☐ NO ☐

If YES, then what is your typical treatment plan? (check all that apply)

If you answer "yes" more than once, please rank order each treatment (1=most often, 10=least often)

	Yes ☒	Numbering (1-10)
a. Painkillers	☐	____
b. Antibiotics	☐	____

(penicillin / amoxicillin-clavulanate / broad spectrum antibiotics)

Please specify the name, dosage and duration of antibiotics you have commonly used:

_____

	Yes ☒	Numbering (1-10)
c. Topical antibiotics	☐	____
d. Systemic steroids	☐	____
e. Nasal steroids	☐	____
f. Oral antihistamine	☐	____
g. Decongestants	☐	____
h. Nasal douche	☐	____
i. Steaming	☐	____
j. Mucolytics	☐	____
k. Herbal medicine	☐	____
l. Others (specify) _____	☐	____

4. In general, do you treat patients with rhinosinusitis with moderate symptoms (no fever, no severe pain) which persist *more* than 5 days? YES ☐ NO ☐

If YES, then what is your typical treatment plan? (check all that apply)

If you answer "yes" more than once, please rank order each treatment (1=most often, 10=least often)

	Yes ☒	Numbering (1-10)
a. Painkillers	☐	____
b. Antibiotics	☐	____

(penicillin / amoxicillin-clavulanate / broad spectrum antibiotics)

Please specify the name, dosage and duration of antibiotics you have commonly used:

_____

	Yes ☒	Numbering (1-10)
c. Topical antibiotics	☐	____
d. Systemic steroids	☐	____
e. Nasal steroids	☐	____
f. Oral antihistamine	☐	____
g. Decongestants	☐	____
h. Nasal douche	☐	____
i. Steaming	☐	____
j. Mucolytics	☐	____
k. Herbal medicine	☐	____
l. Others (specify) _____	☐	____

5. In general, do you treat patients with rhinosinusitis with severe symptoms (with fever >38°C o severe pain)? YES ☐ NO ☐

If YES, then what is your typical treatment plan? (check all that apply)

If you answer "yes" more than once, please rank order each treatment (1=most often, 10=least often)

	Yes ☒	Numbering (1-10)
a. Painkillers	☐	____
b. Antibiotics	☐	____

(penicillin / amoxicillin-clavulanate / broad spectrum antibiotics)

Please specify the name, dosage and duration of antibiotics you have commonly used:

_____

	Yes ☒	Numbering (1-10)
c. Topical antibiotics	☐	____
d. Systemic steroids	☐	____
e. Nasal steroids	☐	____
f. Oral antihistamine	☐	____
g. Decongestants	☐	____
h. Nasal douche	☐	____
i. Steaming	☐	____
j. Mucolytics	☐	____

k. Herbal medicine ☐ ____

l. Others (specify) _____ ☐ ____

6. What criteria do you typically use for referring each of the following types of rhinosinusitis patients to an ENT specialist?

a. Patients with moderate symptoms (choose one)

- ☐ Always refer them to a specialist right after diagnosis
- ☐ When no improvement occurs after 14 days of treatment
- ☐ When no improvement occurs after 4 weeks of treatment
- ☐ After one course of antibiotic treatment which did not work
- ☐ After 48 hours with no effect of intranasal corticosteroids and/or antibiotics
- ☐ Never refer them to a specialist
- ☐ Other (specify):_____

b. Patients with severe symptoms (fever,pain) (choose one)

- ☐ Always refer them to a specialist right after diagnosis
- ☐ When no improvement occurs after 14 days of treatment
- ☐ When no improvement occurs after 4 weeks of treatment
- ☐ After one course of antibiotic treatment which did not work
- ☐ After 48 hours with no effect of intranasal corticosteroids and/or antibiotics
- ☐ Never refer them to a specialist
- ☐ Other (specify):_____

c. Patients with ocular or neurological complications (choose one)

- ☐ Always refer them to a specialist right after diagnosis
- ☐ When no improvement occurs after 14 days of treatment
- ☐ When no improvement occurs after 4 weeks of treatment
- ☐ After one course of antibiotic treatment which did not work
- ☐ After 48 hours with no effect of intranasal corticosteroids and/or antibiotics
- ☐ Never refer them to a specialist
- ☐ Other (specify):_____

7. Can we call you for an interview by telephone with 3 cases. This will take approximately 20 minutes. **YES** ☐ **NO** ☐

Telephone: _____

Thank you very much for your cooperation in this survey!

Chapter 4

Antibiotics for rhinosinusitis

Chapter 4.1

Complications of acute rhinosinusitis in The Netherlands

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Abstract

Background

Despite the evidence demonstrating that antibiotics are of little benefit in acute rhinosinusitis (ARS), general practitioners continue to prescribe them, possibly in an attempt to prevent potentially dangerous complications. In this study we present epidemiological data about the incidence, course and severity of such complications in the Netherlands.

Methods

This retrospective cohort study included all patients hospitalised in the Netherlands in 2004 with a complication of ARS. Records were made of the symptoms of ARS and the complication, demographics, medical history, medical treatment preceding hospitalisation, diagnostic techniques, therapeutic management, course and outcome.

Results

Forty-seven patients with 48 complications (16 intracranial, 32 orbital) were included. In the intracranial group (mean age 35.9 years) 6 patients had been treated with oral antibiotics prior to hospitalisation. While hospitalised, all patients were treated with intravenous antibiotics and 15 underwent surgery. Eight patients recovered fully after treatment, three patients had residual symptoms, 3 patients died (missing data: 2).

Of the 31 patients with orbital complications (mean age 17.4 years), 14 received oral antibiotics before admission. While hospitalised, all patients were treated with intravenous antibiotics and 13 underwent surgery. Twenty-seven patients recovered fully and 2 had residual symptoms (missing data: 2).

Conclusions

Severe ARS complications occur in an otherwise healthy population in an estimated 1:12,000 paediatric and 1:32,000 adult cases in the Netherlands. Our study suggests that antibiotic treatment of acute rhinosinusitis in general practice does not play a role in preventing complications.

Introduction

Acute rhinosinustis (ARS) is one of the commonest diagnoses made in primary care, and its management has significant implications for both public health and costs: multiple meta-analyses [1-3] have shown the limited benefits conferred by routine antibiotic prescription in the general population. Interestingly, despite the evidence of the lack of benefit of blanket antibiotic use in ARS, prescribing patterns vary widely between countries, ranging from 70% [4] to 99% [5]. The Netherlands has one of the lowest (if not the lowest) antibiotic prescription rates in primary care in Europe [6] (and correspondingly, one of the lowest rates of bacterial resistance [7]).

To manage patients with rhinosinusitis, general practitioners in The Netherlands generally use the guideline from the Dutch College of General Practitioners. The treatment is based on the severity of the symptoms and the risk of developing complications. It advises to start with symptomatic treatment. This guideline states that antibiotics are not indicated for the normal course of ARS [8]. A recent questionnaire-based study showed that 34% of Dutch general practitioners (consider to) prescribe antibiotics for moderate ARS. In case of severe ARS this percentage increases to 84% [9].

However, informed decision about the risk of using antibiotics (or not) must also take into account the potential effect of antibiotics as well as the incidence of rare but potentially serious sequelae of ARS, including orbital and intracranial complications. **Box 1** lists early symptoms of complications of ARS justifying immediate referral to specialist care [10]. A balanced cost/benefit analysis requires accurate epidemiological data that documents the incidence, course and severity of these complications. This study presents data of this kind from the Netherlands.

- Periorbital oedema
- Displaced globe
- Double vision
- Ophthalmoplegia
- Reduced visual acuity
- Severe unilateral or bilateral frontal headache
- Frontal swelling
- Signs of meningitis or focal neurological signs

Box 1. Symptoms of complications of ARS justifying immediate referral/hospitalisation

Methods

This retrospective cohort study looked at the medical files of patients hospitalised in Dutch hospitals in 2004 with a complication of acute rhinosinusitis. We used hospital data from the National Medical Register (Landelijke Medische Registratie, LMR). The Prismant research institute provided all the data. The LMR contains data about admissions in general and academic hospitals in the Netherlands. This information includes medical data such as diagnoses, as well as patient-specific data, including age, gender and date of admission. The LMR is based on the ICD-9 classification and procedures from the Dutch Classification System of Procedures. There were no major changes to these classification systems between 1991 and 2006. Participation in the LMR is voluntary. In 2004, the participation percentage of hospitals in the LMR was 98%. We requested data about all patients admitted to a hospital in 2004 with a possible complication of ARS. To ensure we would not miss certain complications, we selected a wide range of diagnoses that could represent ARS complications (**Appendix A**). On the basis of this database, hospitals were visited to handsearch patient files for additional data.

The symptoms of both ARS and the complications were recorded, as well as demographics, medical history, medical treatment preceding hospitalisation, diagnostic techniques, therapeutic management, course and outcome.

Results

The Prismant database provided us with hospitalisation data relating to 488 patients with a possible complication of acute rhinosinusitis in 2004. After excluding 69 duplicate cases, the number was reduced to 419 cases. In 94 cases, it was not possible to assess the medical file, either because the hospital did not cooperate with this study or because the patient could not be identified due to incorrect identification numbers or for other reasons. As a result, 324 patient files were available and studied.

In 278 of these 324 potential cases there was no clinical or radiological evidence of ARS in the patient either before or during hospitalisation. The most frequently encountered diagnosis in these 278 patients was meningitis (86 cases). The second most common diagnosis was intracerebral abscess with a non-sinogenic focus, for example otitis media. In some patients an obvious focus of infection was not identified, but these patients had no symptoms of ARS on clinical or radiological examination. These patients were therefore excluded from this study (see **figure 1** for a flowchart). The reader is referred to appendix B for the characteristics of the excluded patients.

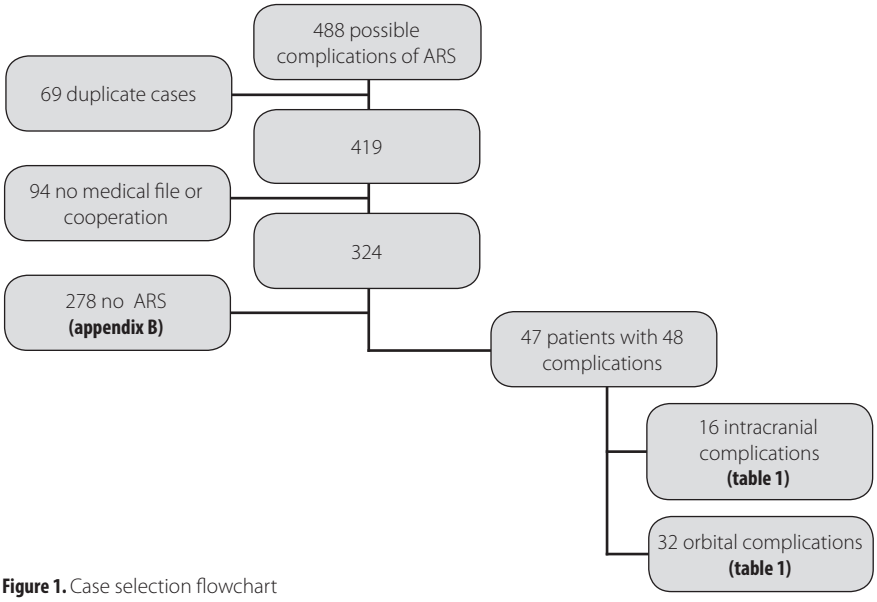

Figure 1. Case selection flowchart

Forty-seven patients were identified, with 48 complications of ARS. The observed complications were divided into two groups: intracranial and orbital (see **table 1**). These two groups will be discussed separately in the remainder of this article.

Table 1. Complications of ARS

Diagnosis	Total number of patients	Children	% (percentage of total)
Intracranial	16	5	100%
Subdural empyema	9	4	56%
Meningitis	3	0	19%
Intracerebral abscess	2	1	13%
Epidural empyema	1	0	6%
Encephalitis	1	0	6%
Orbital	32	21 (22 complications)	100%
Orbital cellulitis	14	13	47%
Pre-septal cellulitis	12	6	34%
Subperiostal abscess	4	2	13%
Intra-orbital abscess	2	1	6%

Intracranial complications

Sixteen patients had intracranial complications of ARS: 13 of them were males aged 5 to 77 years (mean 35.9 years). Five patients were younger than 18. Two patients (12%) were diabetic and/or immunocompromised. Six patients had a known ENT history; two were smokers. **Table 2** contains details about the medical histories.

Table 2. Medical history

	Intracranial complications			Orbital complications		
	Yes	**No**	**Unknown**	**Yes**	**No**	**Unknown**
Diabetes mellitus	2	11	3	0	19	12
Immunocompromised	1	11	4	0	19	12
Smoking	1	9	6	2	23	6
CRS with/without nasal polyps	3	13	16	5	19	38
Recurrent ARS	3	4	9	9	6	16
Facial trauma	2	4	10	0	13	18
Nasal/Paranasal surgery	1	6	9	5	8	18

Although all patients were diagnosed with ARS on hospitalisation, only 8 of them (50%) reported experiencing symptoms of ARS in the days preceding admission. These patients most commonly complained of purulent rhinorrhoea, headache and fever.

Six patients (37%) had been treated with oral antibiotics prior to hospitalisation for 4.5±3.3 days (adults: 4.0±0, children: 5.0±5.7). Five of these patients had complaints of ARS. Three patients with complaints of ARS were not treated with antibiotics. Five different agents were prescribed: amoxicillin(3), doxycyclin(2), azitromycin(2), ciproxin(1) and co-trimoxazol(1).

The most frequently encountered symptoms of intracranial complication upon presentation to the hospital were diminished consciousness and headache. Intracranial and sinus abnormalities were seen on all CT (15) and MRI scans (6) made. In all of these cases, there was opacification of at least one sinus. A pansinusitis was found at least on one side in 9 patients. In four (all adults) out of sixteen patients, dehiscence of the posterior wall of the frontal sinus was seen (due to a mucocele in one case). A defect in the ethmoidal roof was found in one adult patient, and a partial thrombosis of the superior sagittal sinus in another.

Sinus aspirate was cultured in 7 cases, blood cultures were performed in 6 cases and cultures of spinal fluid after lumbar puncture were made in 7 patients. **Table 3** shows the results of these cultures. The results matched in one of the three patients with both CSF and sinus fluid cultures. Both sinus fluid and blood were cultured in 4 patients. The results matched in 3 patients.

Table 3. Cultures

Intracranial complication	**N**
Sinus culture	7
S. Intermedius	2
S. Milleri	1
S. Pneumoniae	1
Peptostreptococcus Micros	1
Corynebacterium Xerosis	1
Coagulase-negative Staphylococus	1
Anaerobes	1
Fusobacterium Varium	1
Blood culture	6
S. Pneumoniae	1
Peptostreptococcus Micros	1
Fusobacterium Varium	1
Coagulase-negative Staphylococus	1
No bacteria	2
Lumbar puncture	7
S. Pneumoniae	3
S. Milleri + H. Parainfluenza	1
Unknown micro-organism	2
No bacteria	1

Orbital complication	**N**
Sinus culture	3
S. Intermedius	1
S. Aureus	1
No bacteria	1
Blood culture	10
Coagulase-negative Staphylococus	1
No bacteria	9

All patients were treated with intravenous antibiotics for a mean of 32.2±18.5 days (adults: 28.1±19.2, children: 46.5±3.5) with 2.9±1.2 different antibiotic agents. In two cases, intravenous treatment consisted of one single antibiotic: benzylpenicillin in one case, an unknown antibiotic in the other. Five patients were treated with

two antibiotic agents. Nine patients were treated with 3 or 4 different antibiotics simultaneously. Metronidazole was used in all but one of these cases. In addition to antibiotic therapy 11 patients received systemic corticosteroids, 9 patients were given anti-epileptic medication, 8 patients (4 children) were treated locally with saline nasal douches and/or xylometazolin nose drops and all but one patient (an adult who had encephalitis without abscess) underwent surgery. **Tables 4** and **5** list the diagnoses, together with the associated neurosurgical and rhinological management.

Table 4. Surgical management of intracranial complications of ARS

Diagnosis (n)	Rhinological surgical treatment (n)	Neurosurgical treatment (n)	Other surgical treatment (n)
Subdural empyema (9)	Sinus drainage (6)	Drainage empyema (8)	
Meningitis (3)	Sinus drainage (3)	Ventricle drain (1)	Tracheotomy (1)
Intracerebral abscess (2)	Sinus drainage (1)	Drainage empyema (2) Ventricle drain (1)	
Epidural empyema (1)	Sinus drainage (1)	Drainage empyema (1)	
Encephalitis (1)	No surgery	No surgery	

Table 5. Surgical management of orbital complications of ARS

Diagnosis (n)	Rhinological surgical treatment (n)	Orbitosurgical treatment (n)
Orbital cellulitis (13)	Sinus drainage (5)	Orbital decompression (1)
Pre-septal cellulitis (12)	Sinus drainage (2)	Orbital decompression (1)
Subperiostal abscess (3)	Sinus drainage (2)	Orbital decompression (1) Drainage abscess (1)
Intra-orbital abscess (3)	Sinus drainage (2)	Drainage abscess (2)

Eight patients (50%) recovered fully after treatment, three patients (19%) had residual symptoms after dismissal from the hospital. Two of these three patients were children with pansinusitis complicated by subdural empyema. The third patient was an adult with meningitis secondary to maxillary sinusitis and herpes. All were treated with intravenous antibiotics, antiepileptic medication and neurosurgical surgery. One child did not undergo ENT surgery. The two children had mild dysphasia after dismissal; the adult patient suffered from polyneuropathy. In 2 cases the outcome is unknown and 3 patients (19%) (all males, aged 18, 62

and 77) died. The youngest patient, a previously healthy man, died of a massive pulmonary embolus 6 days after the sinuses and subdural empyema were surgically drained. The oldest patient had significant comorbidity, including Kahler's disease, for which he was undergoing chemotherapy, as well as diabetes and hypertension. He was admitted with encephalitis against a background of uncontrolled diabetes and immunosuppresion. Despite antibiotic therapy he went into a coma and died eight days after admission. The third patient (male, age 62) was admitted with epileptic seizures and was subsequently diagnosed with an intracerebral abscess which ruptured into the cerebral ventricles after remaining undiagnosed for 18 days. Despite repeated surgery (placement of ventricular and intracranial drain, drainage of the abscess) he fell into a coma and mechanical ventilation was discontinued after six weeks.

Table 6 provides an overview of the total number of complications and management, including the numbers for children.

Table 6. Complications and management

	Intracranial		Orbital	
	Total	**Children**	**Total**	**Children**
Number of complications	16	5	32	21
Before hospitalisation				
ENT history	6	1	11	6
ARS symptoms	8	3	20	12
Antibiotics given by GP	6	3	14	5
Diagnostics during hospitalisation				
Sinus aspirate	7	2	3	2
Blood cultures	6	1	0	11
Lumbar punction	7	1	0	0
Therapy during hospitalisation				
I.V. antibiotics	16	5	32	21
Systemic corticosteroids	11	2	4	3
Anti-epileptics	9	3	0	0
Local treatment (nose drops etc.)	8	4	21	14
Surgery	15	5	13	5
Outcome				
Full recovery	8	1	27	17
Residual symptoms	3	2	2	1
Unknown outcome	2	2	2	2
Death	3	0	0	0

Orbital complications

Thirty-two orbital complications were found in 31 patients, 22 of whom were male and 21 children (one child had 2 complications). The age range was 6 months to 74 years (mean 17.4 years). No patients were diabetic or immunocompromised, three had known allergies and two patients were smokers. Eleven patients had an ENT history. **Table 2** lists details about the medical history.

Twenty patients (65%) reported experiencing typical symptoms of ARS in the days preceding admission. Another three children had complaints of headache, fever and malaise without purulent rhinorrhoea. In eight cases it is unknown whether ARS symptoms were present or absent.

Fourteen patients (43%) had been treated with oral antibiotics for 5.2±5.7 days (adults: 6.33±7.1, children: 5.5±6.4) prior to hospitalisation: amoxicillin(4), amoxicillin/clavulanic acid(4), claritromycin(2), flucloxacillin(1), doxycyclin(1) or unknown(2). Seven of these patients did have symptoms of ARS. Thirteen patients with complaints of ARS were not treated with antibiotics prior to hospitalisation. Orbital involvement manifested with swelling (29) and redness (12) of the eyelids, pain in the eye (13), proptosis (8), limitation of eye movement (6) and/or impaired vision (4).

Abnormalities of the sinus and orbit were seen on all CT (23) and MRI scans (7) made. Opacification of one or more sinuses was seen in all patients. Orbital wall defects were found in 3 adult patients, and a maxillary sinus cyst was seen in 2 others (1 child).

Three cultures of sinus aspirate were performed and a blood culture was performed in 11 children. **Table 3** lists the results of these cultures. There were no cases in which a sinus aspirate and a blood culture were taken from the same patient.

After admission to hospital, all patients were treated with intravenous antibiotics. The mean duration of intravenous antibiotic therapy in this group was 6.6±7.6 days (adults: 5.1±1.9, children: 5.3±2.2) with 1.2±0.6 different antibiotic agents. In 29 cases intravenous treatment consisted of a single antibiotic: amoxicillin/clavulanic acid(27), co-trimoxazol(2), cefuroxim(1) or clindamycine(1). One child with orbital cellulitis and ethmoiditis was treated with two antibiotic agents: amoxicillin/clavulanic acid in combination with clindamycine. In addition to antibiotic therapy, 4 patients also received systemic corticosteroids, 21 patients were treated locally with saline nasal douches and/or xylometazolin nose drops and 13 patients underwent surgery (see **table 5**). Twenty-seven patients (87%) recovered fully after treatment. Two patients (6.5%) had persistent proptosis after dismissal from the hospital. In two cases the outcome is unknown. No patients in this group died.

Table 6 provides an overview of the total number of complications and management, including the numbers for children.

Discussion

This study tried to establish the incidence, course and severity of complications of ARS in the Netherlands. We wanted to know whether the low use of antibiotics in the Netherlands led to more ARS complications. Our interest was triggered by the paucity of data on this subject. The paper from Stoll from France showed a very high level of antibiotic use and the paper from van Zuijlen et al. showed that the incidence of acute mastoiditis in the Netherlands is higher than in countries with higher antibiotic prescription rates [11,12].

This analysis confirms the preponderance of youthful and male patients: 65% of patients with orbital complications and 31% of those with intracranial complications were under 18 [13-16] and the male/female ratio was 2.6 [11,13,17-21]. The higher prevalence in males is still unexplained.

It is estimated that Dutch children have 7-10 common colds each year. The estimated frequency for adults is 2-5 episodes per year [10]. As mentioned elsewhere, 0.5-2% of these common colds result in acute bacterial rhinosinusitis (ABRS). In 2004 the Dutch population consisted of 3.6 million children (<18 years) and 12.7 million adults. This results in an estimate of 300,000 (between 126,000-720,000) paediatric and 700,000 (127,000-1,27 million) adult cases of ABRS during this year. We found complications in 25 children and 22 adults, which results in an estimated incidence of complications in 1:12,000 cases a year of ABRS in children and 1:32,000 cases a year of ABRS in adults. Stoll et al. found 43 complications of ARS in a period of 17 months, resulting in an estimated incidence of 30 complications per year. The population served by the hospitals participating in the study by Stoll et al. consists of an estimated 12 million people. If the incidence of ABRS in this French population is the same as in our Dutch adult population the estimated incidence of complications in this French population would then be 30 complications per year mainly in adults in a population of 12 million. This is comparable to the Dutch situation.

The numbers of cases in which symptoms of ARS preceded the complication in our series are comparable to that reported by Stoll et al.: 60% and 63% respectively. In our sample the first symptoms of an intracranial complication were headache and diminished consciousness. This is in accordance with the early symptoms justifying immediate referral as listed in **box 1**. In the group with orbital complications the

most frequently found symptoms were swelling of the eye, redness of the eye and pain in the eye. Interestingly enough, this last symptom is not mentioned in the European position paper on rhinosinusitis and nasal polyps as an alarm symptom requiring instant referral [10]. Our data suggest perhaps it should be.

In Stoll's French series 95% of patients with proven bacterial ARS and 44% of the total patient group were treated with antibiotics before hospital admission. This percentage is comparable with the 42% we found. This relatively low percentage might be caused by the fact that a significant percentage of patients (60%) did not have symptoms of ARS before they were admitted into hospital with the complication. However in our series having symptoms of ARS or not did not influence the prescribing of antibiotics by the GPs significantly. In a British study by Babar-Craig et al., 59% of the patients were treated with antibiotics prior to admission and similar complication rates were seen in patients who were treated with prior antibiotics and those who were not [22].

Most of the patients with complications of ARS were healthy and often young: only two patients were immunocompromised, showing that complications of ARS mainly occur in healthy patients. However, one of the immunocompromised patients died of the complication so there is a risk of serious consequences and therefore a need to start early with antibiotics when a complication has developed.

An intriguing finding is the fact that the common pathogens causing ARS, like Haemophilus Influenzae and Moraxella Catharralis, are underrepresented in our sample. Is this due to the fact that cultures are more often taken in case of fulminant or persistent infection not responding to antibiotic treatment? Or are patients with infections caused by more exotic pathogens truly more prone to developing complications? Or could it be that these common pathogens are already eliminated before the culture is taken? These questions cannot be answered by our data.

Thirty-six percent of patients had a history of nasal or sinus disorder, mainly previous episodes of ARS (26%), nasal/paranasal surgery (13%) and chronic rhinosinusitis with nasal polyps (11%). A French study by Stoll et al.[11] of patients aged 13 or older found an ENT history in almost 50% of cases. They found previous nasal surgery (19%) and facial trauma (16%) to be the most common antecedents, whereas we found the latter in only 4% of patients. This is a finding that raises more questions than it answers: it is clear that patients with previous ENT surgery and CRS are overrepresented in our series. It could be that these patients are at a higher risk of both intracranial and orbital complications, perhaps through minor bony dehiscences created either during the surgery (even though this was not seen, except in one patient with mucocoele) or through the subclinical erosion of the bony plates by the disease. Confirmation of this new finding by other studies

could perhaps lead to different prevention strategies, including a lower threshold for intervention in these patients when they develop ARS.

In this article we presented a retrospective case series. This study design has its limitations like confounding and information bias. The fact that hospital notes are sometimes minimal has resulted in missing data. Because of these limitations, strong conclusions cannot be drawn from our data. However, the above mentioned findings are quite interesting and might stimulate further (prospective) research on the subject. However, groups of subjects in these studies will need to be extremely large, because of the low incidence of complications of ARS.

Conclusions

Severe ARS complications are rare, but they do occur in an otherwise healthy population in an estimated 1:12,000 paediatric and 1:32,000 adult cases in the Netherlands. Severe complications do not seem to be more frequent in this country with very low antibiotic use, compared to countries with high antibiotic prescription rates. Our study suggests that antibiotic treatment of acute rhinosinusitis in general practice does not play a role in preventing complications.

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Appendix A

Search terms National Medical Register

Intracranial diagnoses

Bacterial meningitis

Intracranial and intraspinal abscess

Phlebitis and thrombophlebitis of intracranial venous sinuses

Other encephalitis due to infection classified elsewhere

Nasal diagnoses

Acute nasopharyngitis (common cold)

Acute sinusitis

Orbital diagnoses

Oedema of eyelid

Acute inflammation of the orbit, unspecified

Orbital cellulitis / abscess of orbit

Orbital periostitis

Orbital osteomyelitis

Exophtalmus unspecified

Orbital oedema or congestion

Lateral displacement of the globe

Appendix B

Diagnoses in subjects without ARS

Diagnosis	N	%
Intracranial diagnoses		
Meningitis, non-sinogenic focus	86	30.9
Intracerebral abscess, non-sinogenic focus	41	14.7
Tumour	8	2.9
Sinus thrombosis, non-sinogenic focus	7	2.5
Epidural empyema, non-sinogenic focus	7	2.5
Subdural empyema, non-sinogenic focus	9	3.2
Hemiplegia, non-sinogenic cause	4	1.4
Subdural haematoma	2	0.7
Cerebellar abscess, dental focus	2	0.7
Commotio cerebri	1	0.4
Orbital diagnoses		
Orbital cellulitis, non-sinogenic focus	19	6.8
Orbital abscess, non-sinogenic cause	4	1.4
Periorbital cellulitis	2	0.7
Evisceratio bulbi due to trauma	2	0.7
Other		
Uncomplicated sinusitis	6	2.2
Otitis media	4	1.4
Ulcerative skin lesions	2	0.7
Mucocele	1	0.4
Furunkel nasi	1	0.4
Sinus cyst	1	0.4
Trigeminal nerve neuralgia	1	0.4
Sepsis	1	0.4
Tracheo-/bronchomalacia	1	0.4
Unknown	66	23.7
Total	**278**	**100**

Chapter 4.2

Avoid prescribing antibiotics in acute rhinosinusitis

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Acute rhinosinusitis (ARS) is an acute inflammatory condition of the nose and sinuses that is characterised by sudden nasal blockage, discharge, facial pain, or pressure and reduction in smell in adults or cough in children [1]. It is common, having a global prevalence of 6-15% [1,2], and it is usually managed in primary care. Despite consistent evidence of spontaneous resolution and recommendations to restrict antibiotics to severe illness, more than 80% of people with mild ARS receive antibiotics in Europe and North America [2-5]. Prescription rates might be lower (30%) in Asia, although over the counter availability of antibiotics in some settings makes accurate figures difficult to ascertain [2]. High prescribing results in pressure for antibiotic resistance and in adverse events. However, the primary cause of ARS is postviral inflammation. Fewer than 2% of patients have the more severe presentation of "bacterial ARS", a clinical rather than microbiological diagnosis characterised by discoloured discharge, severe local unilateral pain, fever (>38ºC), raised levels of inflammatory markers (erythrocyte sedimentation rate and C reactive protein) and/or "double sickening" (deterioration after an initial milder illness) [1]. The gold standard diagnostic test of true bacterial ARS is a positive culture from an invasive sinus puncture or meatal swab (ideally endoscopically guided); radiological opacification of the sinuses has less diagnostic value. Neither bacteriology nor radiology is recommended in making the clinical diagnosis of bacterial ARS or guiding management. Individual symptoms are poorly predictive, but there is limited evidence to suggest that combinations of clinical factors (while not diagnostic of bacterial infection) may alert clinicians to patients with more severe and prolonged illness—for example, lasting beyond 10 days or worsening after 5-7 days—who should be monitored and considered for more intensive treatment, including antibiotics [6-8].

The diagnostic criteria for bacterial ARS are similar between guidelines, derived from expert consensus and observational data, and **box 1** outlines two examples [1,8]. These centre on the severity, character, and duration of symptoms as cited above. About a third of those with a clinical diagnosis of ARS will have bacteria identified on endoscopic sampling [9], and most of these people will recover fully without antibiotic treatment. No controlled trials have shown that even bacterial ARS requires an antibiotic, although placebo controlled studies might be deemed unethical in those with a more severe illness. All current guidelines state that the combination of at least three of the severe symptoms and signs listed in **box 1** should make the clinician at least consider antibiotic treatment [8,10]. We propose avoiding prescribing antibiotics in ARS unless several of the features given in **box 1** are present.

Bacterial ARS is characterised by the presence of at least three of the following symptoms in European guidelines [1]:

- Discoloured discharge (with unilateral predominance) and purulent secretion in the nasal cavity
- Severe local pain (with unilateral predominance)
- Fever (>38º C)
- Raised erythrocyte sedimentation rate or C reactive protein
- "Double sickening"—that is, a deterioration after an initial milder phase of illness

Diagnosis of bacterial ARS requires the presence of at least two of the following symptoms, which must include item 2 or 3, and symptoms persisting beyond 10 days or worsening after 5-7 days in Canadian guidelines:[8]

1. Facial pain, pressure or fullness,
2. Nasal obstruction,
3. Nasal purulence or discolored postnasal discharge,
4. Hyposmia or anosmia

Box 1. Combinations of clinical factors that may indicate more severe disease and consideration of antibiotic therapy

The evidence for change

Systematic reviews show that uncomplicated ARS resolves without antibiotic treatment [11,12]. A Cochrane review of antibiotics against placebo in adults with ARS found 10 trials (eight from primary care) with a low risk of bias, involving 2450 participants. Antibiotics provided no meaningful benefits; they can marginally shorten the time to cure (by less than half a day), but only five more participants per 100 will be cured by 7-14 days, and 18 participants (95% confidence interval, 10 to 115) will need to be treated for one patient to be cured more quickly. This needs to be weighed against adverse effects of antibiotics—the number needed to treat to harm was only 8 (95% confidence interval 6 to 13) [12] with the most common adverse events being gastrointestinal disturbances (nausea, vomiting, diarrhoea) and rash. Serious adverse events were uncommon in both arms. Given the lack of clear benefits and the pressing global problem of antibiotic resistance [13], the authors state: "there is no place for antibiotics for the patient with clinically diagnosed, uncomplicated acute rhinosinusitis."

A separate Cochrane review of antibiotics versus placebo for acute maxillary sinusitis (a common subgroup of ARS) with symptoms lasting at least seven days [14] found six controlled trials. There was a modest symptom resolution benefit with antibiotics, but improvement was high in both the placebo (80%) and the antibiotic treated groups (90%). There was also only a marginal difference in "total cure" rates between groups, with antibiotics resulting in a small reduction in relative risk of ongoing symptoms at 7 to 15 days (0.73, 0.63 to 0.85). The authors conclude that the modest benefits must be weighed against the potential for adverse effects at

both individual and population levels.

The evidence shows that in a primary care setting, antibiotics have little if any role in ARS in adults and only a small treatment effect in patients with severe symptoms that persist beyond a week [14].

Non-antibiotic treatment options include information on disease course, reassurance, and symptomatic treatment. Although widely used, there is no convincing evidence of clinically relevant benefits from antihistamines, steam inhalation, decongestants, or saline irrigation [1,15]. Topical nasal steroids have been shown to have a modest effect on symptoms and speed of recovery [16]. A Cochrane review found that symptoms of participants receiving this treatment were more likely to resolve at two weeks compared with those receiving placebo (73% v 66.4%; risk ratio 1.11, 1.04 to 1.18). This modest benefit is similar to that observed for antibiotics. Although this review reported no significant adverse events, possible adverse effects can include nasal irritation and epistaxis [17,18]. Current topical nasal steroid preparations are not licensed for this indication.

Barriers to change

Doctors want to prevent serious complications of ARS, such as orbital or intracranial abscess, which represent medical emergencies requiring prompt recognition and treatment. Clinical case series from specialist units treating these complications, however, suggest that they occur rarely and early in the course of the disease, and that the prevalence and the outcome are not influenced by early antibiotics in primary care [19,20].

Research evaluating drivers for overprescribing antibiotics in respiratory tract infections suggest uncertainty in diagnosis and management, perceptions of patient expectation and potential conflict with patients [21], availability of antibiotics over the counter [22], and unawareness of local resistance problems [23] are important. Professional education and communication training, with or without additional near patient C reactive protein testing, can substantially reduce antibiotic use in respiratory infections [24].

How should we change our practice?

Antibiotic treatment should not be used in adults with uncomplicated ARS, and we propose that it should only considered for the small minority with features

such as high fever, severe (unilateral) facial pain, purulent rhinorrhoea and "double sickening" [1].

Non-antibiotic treatment strategies centred on symptom control and the provision of information on the inflammatory but non-bacterial self limiting nature of the disease, and the lack of benefit and potential harm of antibiotics, should be usual first line management, for both individual and population health considerations.

Key points
Only consider prescribing antibiotics in patients with symptoms of acute rhinosinusitis (ARS), for instance with at least three of the following more severe symptoms: purulent secretion, high fever, severe (unilateral) facial pain, prolonged illness (7 days or more), and/or "double sickening."
The prescription of antibiotics does not prevent serious complications in ARS

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Chapter 5

General discussion

Rhinosinusitis is one of the commonest diagnoses in healthcare resulting in significant impact on health care expenditure [1-3]. One should realize that acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) are two different diseases (**chapter 1**). The most important differences are that ARS is infectious, short of duration and mostly self-limiting, while CRS is a multifactorial, chronic inflammatory disease. CRS is most likely not a result of prolonged ARS. CRS is underrecognized, despite its prevalence, impact on quality of life and healthcare costs and also compared to other chronic diseases like asthma [4]. In this thesis we evaluated rhinosinusitis in the general population and in the Dutch health care system (primary and secondary/tertiary care).

Epidemiology of rhinosinusitis and allergic rhinitis

In the Netherlands, data on the incidence and prevalence of ARS and CRS and referral patterns in primary and secondary care are very limited. Therefore, we evaluated the prevalence of ARS and CRS in the general population (**chapter 2.1**) and appraised available data in primary care (**chapter 3.1**).

In the general Dutch population, we found a prevalence of 18% for ARS and 16% for CRS (**chapter 2.1**). For Europe, the GA^{2}LEN survey has shown significant variation in the prevalence of epidemiologically defined CRS with prevalences ranging from 7-27% [5]. The reason for these differences are unclear. We evaluated the potential role of risk factors such as allergic rhinitis (AR) and asthma, adverse response to painkillers, occupation, ethnicity, smoking exposure, age, and gender and measured these in three different areas of The Netherlands. We found a number of the above-mentioned factors of relevance for CRS but not place of residence, gender or occupation. This is in contradiction to some other studies [6-9].

We hoped to find differences based on place of residence and living conditions by comparing two places in the Amsterdam vicinity with very different living conditions and one place in the east of the Netherlands. We could not find any relevant differences, which makes an obvious effect of living conditions and pollution less likely but not impossible.

Interestingly, we found Caucasians to be at lower risk for CRS than most of the other ethnicities (**chapter 2.1**). However, the only other comparable study in the U.S. recently found the opposite: higher odds of CRS in whites compared to non-whites [10].

For epidemiology of rhinosinusitis in the Dutch primary care system, we used data from two different morbidity registrations used by general practitioners (GPs) from 1985 to 2002 or 2006 (**chapter 3.1**). For ARS and CRS combined, a prevalence of 19.1/1000 patientyears was found. The incidence of rhinosinusitis was 18.9 or 28.7/1000 patientyears, depending on which morbidity registration was used. According to NIVEL (Nederlands Instituut voor onderzoek in de gezondheidszorg, Dutch Institute for health care research), the incidence of rhinosinusitis in primary care was 25/1000 patientyears in 2016, while the prevalence was reported to be 21/1000 patientyears [3]. This indicates that the numbers we found seem to be stable over the years. There is only a small difference between the incidence and prevalence, indicating that rhinosinusitis in this registration is not considered a chronic condition. We conclude that ARS is registered as "rhinosinusitis". CRS is either not recognized or registered elsewhere (using another diagnosis code).

In the general population study, we used a cross-sectional study based on clear definitions of symptomatology according to EPOS [11]. However, comparison of the prevalence of ARS and CRS we found in the general population to the prevalence in primary care is complicated by difficulties in the two GP registration systems. Firstly, the definition of ARS and CRS was not consistent between the two databases used and not consistent with the definition according to EPOS [11]. Secondly, the population of a general practice differs yearly. To express the prevalence, we had to use patientyears. This means that every patient that has been in the general practice for one year is responsible for one patientyear. Some patients may have been in the general practice during the whole period of the registration, but some other patients may have been in the practice for only one or two years. So, 10 patientyears can account for 1-10 patients. This makes comparison with the percentages found in de GA^{2}LEN survey difficult. To compare the prevalence of (symptom-based) rhinosinusitis in the general population with the registered diagnosis of rhinosinusitis in general practice, we need to know the prevalence in the general practice in one specific year together with the exact number of patients in the registration in that year. Unfortunately, we do not have these data. Still, we can make an estimation based on the data in the morbidity registrations we used. In the CMR (Nijmegen Continuous Morbidity Registration) 3244 patients were registered with ARS in a period of 22 years. The average population consisted of approximately 12000 patients. An estimated percentage can then be calculated: (3244/22/12000)*100%=1,2%. For the TP (Transition Project) database this means: 5424 patients with ARS/18 registration years/18000 patients in the practice*100%=1,7%. Taking into account the variable population, the percentages are probably even lower than estimated above. Logically, we expected the number of patients with ARS (and CRS) to be lower in general practice than in the general population, because not all patients will visit their GP for these complaints. But

these numbers are extremely low compared to the 18% we found in the general population. From the survey used in **chapter 2.1**, we know how many participants in the general population report to have a doctor's diagnosis of CRS, but not of ARS. Furthermore, participants may have visited their GP for their nasal symptoms, but were not diagnosed with rhinosinusitis or did not hear this diagnosis from their GP. Furthermore, we depend on the diagnosis (and coding) that GPs put into the registration system. Despite these limitations, chronic rhinosinusitis indeed seems to be underrecognized, already in the primary care system.

We can compare some other data between our studies in general population and in primary care. In the general population, we found females to be at higher risk for ARS than males. This is consistent with the findings from the GP morbidity registrations (for ARS and CRS together). But this difference in general practice may be a result of females consulting their GP more often than men [12]. For CRS we did not find this difference between men and women in the screening survey. Furthermore, the relation of AR with ARS/CRS was found in all of the studies in this thesis [13,14].

In the NIVEL registration mentioned before, the prevalence of AR in primary care in 2016 was 51/1000 patientyears and the incidence 24/1000 patientyears. Here, there is quite a big difference between incidence and prevalence, indicating a chronic condition [3]. Our population-based study (**chapter 2.1**) indicates a prevalence of AR of 29%. This is based on what the participants report. This is in line with a study in which positive skin pricktests (tree mix, grass mix and housedustmite) in combination with corresponding symptoms were found in about 31% of the population in a random group of 2320 patients [15]. In another study in the Danish general population, 30% of the participants had a positive skin prick test, 23% was diagnosed with AR (positive skin prick test combined with symptoms) and only 57% of them was diagnosed with hay fever by their doctor [16].

Diagnosis and differential diagnosis of rhinosinusitis

Diagnosis of rhinosinusitis mainly depends on symptomatology. In primary care, the vast majority of GPs report to distinguish ARS from CRS (96%), although the correct parameter (duration of complaints shorter or longer than 12 weeks) is used by only half of them (**chapter 3.2**). As we have shown in **chapter 2.2**, there is a fair correlation between symptoms with findings on physical examination, as roughly two thirds of the patients with an (EPOS) epidemiological diagnosis of CRS had abnormalities at endoscopy. As such, correct diagnosis in primary care should be possible by anamnestic data only (accepting a limited overestimation).

To determine how accurate the diagnosis of CRS in primary care or emergency setting is, a study was performed in the USA. Retrospectively, this study analyzed whether patients diagnosed with CRS (ICD-9) by non-otolaryngologists actually met the criteria for CRS by Lanza (in 1997, before EPOS) [17]. These criteria included 12 weeks of a combination of symptoms (pain, facial fullness/pressure, nasal obstruction, purulent rhinorrhea, hyposmia, and visible purulence on examination). Only 1 of 114 patients actually met these criteria. Most patients did not meet the criteria because of the duration of symptoms (too short). But this depended on the documented duration of symptoms, which was not always perfectly clear. Only 23% had a CT scan of the head or sinuses. None of the caregivers noted any information on examination of the middle meatus [18]. Although in the morbidity registration evaluated in **chapter 3.1** it was indicated that more than 90% of the patients was physically examined, we fully understand the limited possibilities of GPs to perform examination of the middle meatus in daily practice. As mentioned before, we do not think this physical examination is mandatory for proper diagnosis in primary care. If diagnosis is based on duration of relevant (EPOS) symptomatology rather than that a lot of emphasis is placed on the difficult/impossible proper physical examination of the middle meatus, misdiagnosis will decrease.

Careful symptom-based diagnosis of rhinosinusitis also guides the GP through the differential diagnoses. Distinguishing chronic upper airway diseases like AR and CRS may at first sight present difficulties as patients with both diseases usually complain of nasal obstruction and rhinorrhea. However, other symptoms like itch and sneezing in AR and facial pain and loss of smell in CRS are more disease specific. Although in the definitions of both diseases the duration is slightly different (from > 4 weeks in persistent AR to > 12 weeks in CRS), both diseases are clearly separated in their (chronic) duration from acute upper airway disease like common cold and ARS. This differentiation therefore is easy to make and very relevant because it determines the management plans, being symptomatic or (in selected cases) antibiotics in acute, and anti-inflammatory in chronic disease [11].

To make a correct clinical diagnosis, we can use endoscopy and/or imaging (CT scan). In a Finnish study, the Lund-Mackay scores of CT and MRI were higher in CRSsNP (CRS without polyps) patients compared to AR patients. Endoscopy had limited value in distinguishing CRSsNP from AR. The symptom facial pain/pressure was found to distinguish CRSsNP from AR. However, this study was performed off-seasonally. The article states that controls were volunteers who had AR symptoms but did not have a history of suffering from CRS or acute recurrent rhinosinusitis. But the difficulty exactly is that the history of AR and CRS overlap [19].

In a recent study of Brook, sinus CTs of participants with AR and CRS were compared. They all had an (in vitro) allergen test available. Lund-Mackay (CT-)scores differed significantly between the AR and CRS group, but there was no significant difference in Lund-Mackay scores between positive and negative allergen tests [20]. This indicates that AR has no influence on opacification of the sinuses on CT. And that AR and CRS can possibly be distinguished by CT scans. However, in another study, 20% of healthy controls had mucosal thickening on their CT [21]. As such, abnormalities on CT do not always mean that there are symptoms of rhinosinusitis.

Unfortunately, we do not have CTs of the participants of the GA²LEN Screening Survey.
We do however have some information on nasal endoscopy of the participants. In a follow up of the original GA²LEN Screening Survey, we performed nasal endoscopies in a sample of participants of the Ouderkerk aan de Amstel population and the Ghent population. Of the participants with CRS symptoms, according to the EPOS criteria, circa 2/3 had a positive endoscopy and 38% of the participants without CRS had positive endoscopies (**chapter 2.2**) [22]. This is telling us that patients with symptom-based CRS have a higher risk of abnormal endoscopy, but abnormal endoscopy alone does not always mean that patients actually have CRS. In a Korean study, 88 of 797 participants (11%) with symptom-based CRS from a general population had a positive endoscopy [23]. The lower number of positive endoscopies may be explained by the fact that endoscopy in the latter study was only considered positive in case of mucopurulent rhinorrhea in the middle meatus or nasal polyps while Tomassen et al. also included edema in the middle meatus [22].

In a study of Amine, the sensitivity, specificity, positive predictive value and negative predictive value of endoscopy in patients with at least 2 symptoms of CRS (the 4 possible symptoms being: mucopurulent drainage, nasal obstruction, facial pain-pressure-fullness, and decreased sense of smell) as compared to CT was 36%, 95%, 89%, and 55%, respectively. Fifty-four percent of the patients had a Lund-Mackay score of ≥ 4 on CT and 21,7% had an endoscopy with either polyps in the nasal cavity or middle meatus and/or purulent nasal discharge. Patients with a negative endoscopy were subdivided into 3 groups: a group with 2 out of 4 symptoms for CRS, a group with 3 out of 4 symptoms and a group with all 4 symptoms. The percentage of positive CT-scans increased as the number of symptoms increased (31%, 49% and 63% respectively). Of the 4 tested symptoms, nasal obstruction was found to be most sensitive (91% sensitivity) while hyposmia/anosmia was the least sensitive (48% sensitivity). However, hyposmia/anosmia had both the highest specificity (68%) and positive predictive value (64%) [24].

With a CT as the gold standard for the diagnosis of CRS, the odds ratio for CRS increases significantly when adding endoscopy to symptom-based CRS according to a study of Bhattacharyya [25].

Of the four symptoms used for the epidemiological definition of rhinosinusitis, reduction or loss of smell (especially in combination with other symptoms) is found to be the most important factor predicting a positive nasal endoscopy [26].

The interpretation of endoscopy may be standardized but remains subject to the opinion of the investigator. Previous studies found an interrater agreement variability for nasal endoscopy in CRS and AR, especially concerning edema of the middle meatus [27-30]. This means that we have to be careful with drawing conclusions from endoscopic data. In the light of the mentioned literature and our own data, it seems indeed safe to largely depend on anamnestic data to diagnose a patient with AR. ARS or CRS in primary care.

Considering our advice in **chapter 4.2** to avoid prescribing antibiotics in ARS, it would be interesting to know how viral ARS can be distinguished from bacterial ARS on the basis of symptoms or clinical findings.

In EPOS, bacterial ARS is characterized by at least three of the following symptoms: discolored discharge, severe local (unilateral) pain, fever (>38ºC), raised levels of inflammatory markers (erythrocyte sedimentation rate and C reactive protein) and/or "double sickening" (deterioration after an initial milder illness) [11].

According to the Canadian guideline, bacterial ARS should be considered when symptoms persist beyond 10 days or worsen after 5-7 days. The diagnosis requires the presence of at least two symptoms, which must include nasal obstruction or nasal purulence/discoloured postnasal discharge. Other possible symptoms are facial pain/pressure/fullness and hyposmia/anosmia [31].

For identifying bacterial ARS, symptoms or the change of symptoms have been found to be of little use in a study of Autio. Clinical findings after 9 to 10 days of symptoms like a moderate or profuse (versus none or minimal) amount of secretion in anterior rhinoscopy, secretion seen in the posterior pharynx using a headlight or secretion seen in the middle meatus using an endoscope predicted bacterial ARS more accurately. Furthermore, findings of both facial tenderness and cervical adenopathy moderately predicted a diagnosis of bacterial ARS [32].

Guidelines

In general practice, guidelines of the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG) are frequently used. Unfortunately, there is only a NHG guideline on ARS[33]. Multidisciplinary guidelines on CRS do exist, but we are unsure how extensively these guidelines are used in primary care [34,35]. Therefore, we evaluated to what extent Dutch general practitioners follow the guidelines on rhinosinusitis (**chapter 3.2**).

It is interesting to see how long the NHG guideline on (acute) rhinosinusitis remained unchanged after evidence based international guidelines were published (pointing out the differences in diagnosis and treatment of ARS and CRS) [36,37]. The first report of EPOS for example was published in 2005. In October 2014 the NHG guideline was changed from rhinosinusitis as one disease to ARS only (a NHG-guideline on CRS does not exist) [33]. Since 2007, another separate guideline for CRS exists in the Netherlands (Centraal BegeleidingsOrgaan, CBO-guideline) [34]. But this guideline is probably used less than the better known NHG guidelines.

As the current GP guidelines do not cover the up to date management of rhinosinusitis (both ARS and CRS), it is likely that the management of rhinosinusitis in primary care does not live up to meet international standards. Our data from **chapter 3.2** support this. As this study was performed and published before the new GP guideline on ARS was published in 2014 [33], it would be interesting to see whether management has changed after implementing this new guideline. After introducing the previous Dutch guideline in 2005, Venekamp et al. studied the changes in management of the GPs treating ARS. Only a small decrease in antibiotic prescription was found despite a strong recommendation to restrict the use of antibiotics in ARS [38]. In the US patterns of care before and after publishing the adult sinusitis clinical practice guideline have been studied. Some aspects of care have changed after the new guideline, but some did not. For example, amoxicillin was more often prescribed as first choice antibiotic as was recommended in the guideline. But the prescription of analgetics was unchanged despite recommendations in the guideline [39].

Part of the management of rhinosinusitis is adequate referral to secondary care. The NHG guideline on ARS advises immediate referral in case of reduction of visual acuity, double vision, one painful eye, disturbed eye movement, red or edematous eyelid, swelling of the conjunctiva (chemosis) or exophthalmia, frontal swelling, severe headache (uni- and bilateral), sickness and vomiting, epileptic seizure or reduced consciousness, or neurological symptoms. The only other recommendation for referral (in adults) is advised in case of suspected dentogenous

sinusitis or patients with frequent recurrences (at least three to four episodes per year) [33]. EPOS advises to refer for moderate ARS in case symptoms persist after 14 days of treatment, and after 48 hours of treatment in case of severe ARS. Immediate referral is advised in case of periorbital oedema/erythema, displaced globe, double vision, ophthalmoplegia, reduced vision acuity, sever unilateral or bilateral frontal headache, frontal swelling, signs of meningitis or neurological signs [11].

The CBO-guideline on CRS states that referral is indicated after 4-6 weeks of treatment and in case of symptoms that may indicate involvement of the brain, the eye or a malignant process [34]. Unfortunately, we are not aware of data about Dutch GPs' referral of ARS and CRS patients to secondary care. Therefore, we do not know whether actual referral is based on recommendations of any of the guidelines. As such, we found variable results when we asked GPs when they referred their patients with different stages of ARS and CRS (**chapter 3.2**).

In the Netherlands, GPs are the gatekeepers of healthcare. It is very important that their knowledge is up to date to prevent unnecessary referral and thereby costs. But on the other hand, they have to know when to refer immediately. We found that 88% do refer immediately in case of ocular or neurological complications (**Chapter 3.2**) [40]. It would even be better if the remaining 12% is also aware of the risks of these complications. An updated guideline on ARS and CRS separately would help improving the management of rhinosinusitis.

Antibiotics

We were interested in the (unnecessary) use of antibiotics in the treatment of ARS and whether antibiotics might play a role in the prevention of potential (serious) complications of ARS.

Studies on antibiotics for (acute) rhinosinusitis generally agree on advising to save antibiotics for carefully selected cases. The small therapeutic advantage of a little faster resolution of symptoms does not outweigh the potential adverse events and the risk of bacterial resistance. Fear for complications may drive GPs to easily prescribe antibiotics. The risk of complications of acute rhinosinusitis however is low and may not be influenced by the use of antibiotics [41-45] (**chapter 4.1**).

Looking at prescription of antibiotics, GPs in different countries expose circa half of their patients with ARS to possible overprescribing despite clear recommendations in EPOS. Rhinosinusitis is responsible for the most antibiotic prescriptions in ambulatory care in the United States. Eighty-five percent of the patients with ARS receives a prescription of antibiotics [11,46-48].

In Iceland and Denmark, the appropriateness of prescribing antibiotics for ARS by GPs was studied. Prescribing antibiotics was considered appropriate when there were symptoms for more than 5 days combined with fever. The antibiotic prescribing rate in patients with suspected acute sinusitis was 98,6% in Iceland and 75,5% in Denmark. Respectively 17,8 and 16,4% were considered appropriate prescriptions [49].

A study trying to identify which symptoms of ARS justify the prescription of antibiotics could not draw clear conclusions and states that antibiotics are not justified in cases of ARS without signs suggestive of a serious complication [50]. C-reactive protein testing and/or training in communication skills are found to reduce the amount of antibiotic prescriptions for respiratory tract infections in primary care compared to usual practice [51].

As far as antibiotic prescription behavior is concerned, Dutch physicians do very well. The total outpatient antibacterial use is the lowest compared to the US and 26 other European countries [52-54]. With the chapters of this thesis in mind, prescribing antibiotics for ARS could even be further reduced.

Complications

In secondary care, doctors handle complications of ARS. In **chapter 4.1** we discuss these complications. Especially children are at risk for mainly orbital complications. We found that 43% of the patients with orbital complications were treated with antibiotics before admission. Our findings are in concordance with another study in a tertiary care hospital in which orbital complications were also the most common complications; males had more complications than females [55]. In the US, Benninger found 6 complications out of 10000 cases of ARS. All 6 cases were prescribed antibiotics at their first ARS diagnosis, which confirms our conclusion that antibiotics in ARS do not prevent complications [48].

The fact that complications are more common in males is remarkable, taking into account that (acute) rhinosinusitis seems to be more common in females (**chapter 2.1** and **chapter 3.1**).

Suggestions for future research

It would be interesting to compare the current management of ARS and CRS by GPs with the management as recommended in EPOS for GPs by conducting a

study randomizing GPs in two treatment arms: usual practice (according to the guideline) versus treatment according to the scheme provided in EPOS. The primary endpoint could be the time to symptom resolution compatible with normal daily activities based on symptom scores (rhinorrhea, postnasal drip, nasal congestion/stuffiness, sinus headache and facial pain/pressure/tenderness on palpitation over the paranasal sinuses). Other endpoints can be quality of life, therapeutic response and adverse events. After this study the NHG guideline on ARS can be adapted depending on the results. Nasal corticosteroids are not registered for ARS, but maybe they should be (depending on the results of the above-mentioned study).

We conducted a retrospective study to evaluate the effect of antibiotics on complications of ARS. A prospective study would be even better but is almost impossible. A very large population will be needed to gather enough complications to analyse.

In this digital era, evaluation of direct costs of ARS and CRS in the Netherlands should be easier than before. A retrospective study of a big cohort of patients with a diagnosis of ARS and CRS could be studied. Every step in diagnosis and treatment is documented nowadays. Costs of every step can then be added together. A diverse group of patients is needed, including patients in primary, secondary and tertiary care. Information of patients' insurance can be helpful in this.

Calculation of indirect costs is more difficult but can for example be calculated by counting the days of absenteeism and estimation of loss of productivity.

To make a statement about whether upfront CT for CRS in Dutch healthcare is cost-effective or not, a Dutch study can be conducted. Ideally in a randomised controlled trial. However, it is debatable whether this is medically ethical, given the radiation that comes with CT scanning.

To find out why ethnicity is related to ARS, CRS and AR, further research is needed. Differences may have to do with for example habits, environment or genetics. We need to take into account the exact circumstances in which people live. Such a study should evaluate the habits and environmental factors that may be of influence of certain ethical groups and relate these (in combination with their patient characteristics) to ARS and CRS in a multivariate analysis. Another approach could be to focus on the anatomy of the paranasal sinuses in patients with ARS and CRS of different ethnicities.

Suggestions for daily practice

Some changes in daily practice in primary care can improve the management of rhinosinusitis. Firstly, GPs have to be aware of the differences between ARS and CRS. To support this, there should be a separate (NHG) guideline for CRS. Furthermore, a separate (ICD-10, International Classification of Diseases) code for both diseases should be available in registrations. We advise GPs to base their diagnosis of ARS and CRS on the symptoms described in EPOS [11,35]. There should be no emphasis on physical examination in general practice because proper examination of the middle meatus is hardly possible without an endoscope. Antibiotic prescription should be decreased to an appropriate amount by following the recommendations in EPOS and hopefully in the future in the updated NHG-guidelines.

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Chapter 6

Summary
Nederlandse samenvatting
Portfolio
Curriculum vitae
Dankwoord

Chapter 6.1

This thesis concentrates on rhinosinusitis in the general population, primary care and secondary care. We discuss epidemiology, management and complications of rhinosinusitis.

Chapter 1 – Introduction

Rhinosinusitis is defined as the presence of two or more sinonasal symptoms one of which should be nasal obstruction or nasal secretions, with or without facial pain / headache and smell dysfunction (epidemiological definition). For the clinical diagnosis, it should be combined with consistent nasal endoscopy and/or CT scans when available.

When symptoms have an acute onset and persist for less than 10 days the condition is defined as common cold/acute (viral) rhinosinusitis. When symptoms increase after 5 days or persist after 10 days but not exceed 12 weeks the condition is defined as acute (postviral) rhinosinusitis. When symptoms are present for more than 12 weeks, the condition is diagnosed as chronic rhinosinusitis.

Chapter 2 – Rhinosinusitis in the general population

We assessed the effect of comorbidity, ethnicity, occupation, smoking and place of residence on allergic rhinitis (AR), acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) in chapter 2.1. A questionnaire was sent to a random sample of the Dutch population in three different areas of the Netherlands. A total of 29% respondents met the criteria for AR, 18% for ARS and 16% for CRS. Risk factors for AR were itchy rash, eczema, adverse response after taking a painkiller, asthma, CRS and ARS. Moreover, the risk of AR was twice as low for full-time housewives/ househusbands than for people with jobs. The risk of ARS or CRS was significantly higher in respondents with a doctor's diagnosis of CRS, AR, itchy rash or smoking. The risk of CRS was also significantly higher in respondents with an adverse response after taking painkillers, active smoking or asthma. Furthermore we found differences in the prevalence of AR, ARS and CRS between different ethnicities.

These findings provides support for the belief that ARS, CRS and AR have shared symptoms but are different diseases with different aetiologies.

The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) incorporates symptomatic, endoscopic, and radiologic criteria in the clinical diagnosis of CRS, while in epidemiological studies, the definition is based on symptoms only. In chapter 2.2 we aimed to assess the reliability and validity of a symptom-based definition of CRS using data from the GA^{2}LEN (Global Allergy and Asthma European Network of Excellence) survey. On two separate occasions, 1700 subjects from 11 centers provided information on symptoms of CRS, AR, and asthma. CRS was defined by the epidemiological EPOS symptom criteria (as described above). In two centers, 342 participants underwent nasal endoscopy.

There was a decrease in prevalence of CRS between the two study phases, and this was consistent across all centers. Symptom-based CRS was significantly associated with positive endoscopy in non-allergic subjects, and with self-reported doctor-diagnosed CRS in all subjects, irrespective of the presence of allergic rhinitis. These findings suggest that a symptom-based definition of CRS, according to the epidemiological criteria of EP3OS, is suitable for the assessment of geographic variation in prevalence of CRS.

Chapter 3 – Rhinosinusitis in primary care

To give insight in incidence, comorbidity and interventions taken by the GP in case of rhinosinusitis, two Dutch general practice registration projects were analysed in chapter 3.1. The Continuous Morbidity Registration (CMR) and the Transitionproject (TP) are used to analyse the data on rhinosinusitis in primary practice.

In the CMR 3244 patients are registered with rhinosinusitis. The absolute incidence of (acute) rhinosinusitis is 5191 (18.8 per 1000 patient years). Having nasal polyps is strongest related to rhinosinusitis compared to the other evaluated comorbidities. A separate code for chronic rhinosinusitis exists in this registration, but is not used.

In the TP 5424 patients are registered with rhinosinusitis. Acute and chronic rhinosinusitis are coded as one diagnosis. The incidence of rhinosinusitis is 5574 or 28.7 per 1000 patient years. Patients who visit their GP with "symptoms/complaints of sinus", allergic rhinitis and "other diseases of the respiratory system" have the highest chances to be diagnosed with rhinosinusitis. Medication is prescribed in 90.6 % of the cases.

In the used registries no difference could be made between acute and chronic rhinosinusitis.

To determine whether general practitioners distinguish between ARS and CRS in daily practice and to assess the management of these diseases, a questionnaire about the management of rhinosinusitis, was sent to 1000 GPs in the Netherlands. In chapter 3.2 we discuss the results.

Ninety-six percent discriminated between ARS and CRS. However, their definition of ARS and CRS varied. Fifty-four percent accepted (the EPOS defined) 12 weeks as the division between ARS and CRS. The rest used other definitions. The percentage of GPs prescribing antibiotics rose as rhinosinusitis severity increased. The prescription rate of nasal corticosteroids was highest for CRS. Prescribing nasal corticosteroids in ARS was not very common. The management of rhinosinusitis was not always consistent with the guidelines in place.

Chapter 4 – Antibiotics for acute rhinosinusitis

In chapter 4.1 we present epidemiological data about the incidence, course and severity of complications of ARS in the Netherlands in a retrospective cohort study. We included all patients hospitalised in the Netherlands in 2004 with a complication of ARS.

Forty-seven patients with 48 complications (16 intracranial, 32 orbital) were included. In the intracranial group 6 patients had been treated with oral antibiotics prior to hospitalisation. While hospitalised, all patients were treated with intravenous antibiotics and 15 underwent surgery. Eight patients recovered fully after treatment, three patients had residual symptoms, 3 patients died.

Of the 31 patients with orbital complications, 14 received oral antibiotics before admission. While hospitalised, all patients were treated with intravenous antibiotics and 13 underwent surgery. Twenty-seven patients recovered fully and 2 had residual symptoms (missing data: 2).

We conclude that severe ARS complications occur in an otherwise healthy population in an estimated 1:12,000 paediatric and 1:32,000 adult cases of acute bacterial rhinosinusitis in the Netherlands. Our study suggests that antibiotic treatment of acute rhinosinusitis in general practice does not play a role in preventing complications

In chapter 4.2 we try to make healthcare providers aware of the unnecessary overuse of antibiotics for ARS. To prevent antibiotic resistance and adverse events we advise only to consider prescribing antibiotics in patients with a more severe presentation of bacterial ARS. That is for instance in patients with at least three

of the following more severe symptoms: purulent secretion, high fever, severe (unilateral) facial pain, prolonged illness (7 days or more), and/or "double sickening" (a deterioration after an initial milder phase of illness). Moreover no controlled trials have shown that even bacterial ARS requires an antibiotic. Antibiotic treatment should certainly not be used in adults with uncomplicated ARS.

Chapter 5 – Discussion

We think that some changes in daily practice in primary care can improve the management of rhinosinusitis. Firstly, GPs have to be aware of the differences between ARS and CRS. To support this, a separate guideline for the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG) on CRS should be conducted alongside the already existing guideline on ARS. Furthermore, a separate (ICD-10, International Classification of Diseases) code for both diseases should be available in registrations. We advise GPs to base their diagnosis of ARS and CRS on the symptoms described in EPOS. There should be no emphasis on physical examination in general practice because proper examination of the middle meatus is hardly possible without an endoscope. Antibiotic prescription should be decreased to an appropriate amount by following the recommendations in EPOS and hopefully in the future in the updated NHG-guidelines.

Chapter 6.2

Dit proefschrift concentreert zich op rhinosinusitis in de algemene bevolking, de eerste lijn en de tweede lijn. We bespreken epidemiologie, management en complicaties van rhinosinusitis.

Hoofdstuk 1 – Introductie

Rhinosinusitis wordt gedefinieerd als de aanwezigheid van twee of meer sinonasale symptomen, waarvan één neusobstructie of nasale secretie moet zijn, met of zonder aangezichtspijn / hoofdpijn en reukstoornis (epidemiologische definitie). Voor de klinische diagnose moet dit worden gecombineerd met nasendoscopie en/of CT-scans, indien beschikbaar.

Wanneer symptomen acuut beginnen en minder dan 10 dagen aanhouden, wordt de aandoening gedefinieerd als verkoudheid/acute (virale) rhinosinusitis. Wanneer de symptomen na 5 dagen toenemen of aanhouden na 10 dagen, maar in totaal niet langer dan 12 weken duren, wordt de aandoening gedefinieerd als acute (postvirale) rhinosinusitis. Wanneer symptomen langer dan 12 weken aanwezig zijn, spreken we over chronische rhinosinusitis.

Hoofdstuk 2 – Rhinosinusitis in de algemene bevolking

We bestudeerden het effect van comorbiditeit, etniciteit, beroep, roken en woonplaats op allergische rhinitis (AR), acute rhinosinusitis (ARS) en chronische rhinosinusitis (CRS) in hoofdstuk 2.1. Er werd een vragenlijst gestuurd naar personen die geselecteerd waren door middel van een willekeurige steekproef uit drie verschillende gebieden van Nederland. In totaal voldeed 29% van de respondenten aan de criteria voor AR, 18% aan de criteria voor ARS en 16% aan de criteria voor CRS. Risicofactoren voor AR waren jeukende huiduitslag, eczeem, overgevoeligheidsreactie na het nemen van een pijnstiller, astma, CRS en ARS. Bovendien was de kans op AR tweemaal zo klein voor fulltime huisvrouwen/huismannen als voor mensen met een baan. De kans op ARS of CRS was significant groter bij respondenten met een door een dokter gestelde diagnose van CRS, AR, jeukende huiduitslag of roken. De kans op CRS was ook significant groter bij respondenten met een overgevoeligheidsreactie na het nemen van pijnstillers, actief roken of astma. Verder vonden we verschillen in de prevalentie van AR, ARS en CRS tussen verschillende etniciteiten.

Deze bevindingen ondersteunen de overtuiging dat ARS, CRS en AR gedeelde symptomen hebben, maar dat ze verschillende ziekten zijn met verschillende etiologie.

Het Europees standpunt over rhinosinusitis en neuspoliepen (European Position Paper on Rhinosinusitis and Nasal Polyps, EPOS) gebruikt symptomen en endoscopische en radiologische criteria voor de klinische diagnose van CRS. Terwijl in epidemiologische onderzoeken de definitie uitsluitend op symptomen is gebaseerd. In hoofdstuk 2.2 hebben we de betrouwbaarheid en validiteit van een op symptomen gebaseerde definitie van CRS beoordeeld aan de hand van gegevens uit de "GA2LEN (Global Allergy and Asthma European Network of Excellence) survey". Op twee verschillende momenten verzamelden we informatie over symptomen van CRS, AR en astma van 1700 proefpersonen uit 11 centra. De epidemiologische definitie uit EPOS (zoals hierboven beschreven) werd gebruikt voor de diagnose CRS. In twee centra ondergingen 342 deelnemers een nasendoscopie.

Er was een daling van de prevalentie van CRS tussen de twee studiefasen, en dit was consistent in alle centra. CRS op basis van symptomen was significant geassocieerd met een positieve endoscopie bij niet-allergische patiënten en met door een arts gediagnosticeerde CRS (door patiënten zelf gerapporteerd) bij alle patiënten, ongeacht de aanwezigheid van AR. Deze bevindingen suggereren dat een de epidemiologische definitie van CRS gebaseerd op symptomen (volgens EPOS) geschikt is voor de beoordeling van geografische variatie in de prevalentie van CRS.

Hoofdstuk 3 – Rhinosinusitis in de eerste lijn

Om inzicht te krijgen in incidentie, comorbiditeit en interventies door de huisarts bij rhinosinusitis, werden twee Nederlandse registratiesystemen in de huisartsenpraktijk geanalyseerd in hoofdstuk 3.1. De continue morbiditeitsregistratie (CMR) en het transitieproject (TP) werden gebruikt om de gegevens over rhinosinusitis in de eerste lijn te analyseren.
In de CMR zijn 3244 patiënten geregistreerd met rhinosinusitis. De absolute incidentie van (acute) rhinosinusitis is 5191 (18.8 per 1000 patiëntjaren). Het hebben van neuspoliepen is het sterkst gerelateerd aan rhinosinusitis in vergelijking met andere comorbiditeit. Een aparte code voor chronische rhinosinusitis bestaat in deze registratie, maar wordt niet gebruikt.

In het TP zijn 5424 patiënten geregistreerd met rhinosinusitis. Acute en chronische rhinosinusitis worden gecodeerd als één diagnose. De incidentie van rhinosinusitis is 5574 of 28.7 per 1000 patiëntjaren. Patiënten die hun huisarts bezoeken met "symptomen / klachten van de bijholten", allergische rhinitis en "andere aandoeningen van de luchtwegen", hebben de grootste kans om gediagnosticeerd te worden met rhinosinusitis. Medicatie wordt voorgeschreven in 90.6% van de gevallen.
In de gebruikte registratiesystemen kon geen verschil worden gemaakt tussen acute en chronische rhinosinusitis.

Om te bepalen of huisartsen in de dagelijkse praktijk een onderscheid maken tussen ARS en CRS en om het handelen bij deze ziekten te evalueren, werd een vragenlijst over het diagnosticeren en het handelen bij rhinosinusitis gestuurd naar 1000 huisartsen in Nederland. Hoofdstuk 3.2 geeft hiervan de resultaten weer.
Zesennegentig procent geeft aan een onderscheid tussen ARS en CRS te maken. De definitie van ARS en CRS varieerde echter tussen de verschillende huisartsen. Vierenvijftig procent neemt (de in EPOS gedefinieerde) 12 weken als de afkappunt tussen ARS en CRS. De rest gebruikte andere definities. Het percentage huisartsen dat antibiotica voorschrijft, nam toe naarmate de ernst van de rhinosinusitis toenam. Voor CRS werden de meeste nasale corticosteroïden voorgeschreven. Het voorschrijven van nasale corticosteroïden in ARS was niet erg gebruikelijk. Het handelen bij rhinosinusitis was niet altijd in overeenstemming met de geldende richtlijnen.

Hoofdstuk 4 – Antibiotica voor acute rhinosinusitis

In hoofdstuk 4.1 presenteren we epidemiologische gegevens over de incidentie, het verloop en de ernst van complicaties van ARS in Nederland in een retrospectieve cohortstudie. We hebben alle patiënten die in 2004 opgenomen waren in een ziekenhuis in Nederland met een complicatie van ARS bestudeerd.
Zevenenveertig patiënten met 48 complicaties (16 intracraniale, 32 orbitale) werden geïncludeerd. In de intracraniale groep werden 6 patiënten vóór de opname behandeld met orale antibiotica. Tijdens de opname in het ziekenhuis werden alle patiënten behandeld met intraveneuze antibiotica en werden 15 patiënten geopereerd. Acht patiënten herstelden volledig na de behandeling, drie patiënten hadden restsymptomen, 3 patiënten overleden.
Van de 31 patiënten met orbitale complicaties, kregen er 14 orale antibiotica vóór opname. Tijdens de opname in het ziekenhuis werden alle patiënten behandeld met intraveneuze antibiotica en werden 13 patiënten geopereerd. Zevenentwintig patiënten herstelden volledig en 2 hadden restsymptomen (ontbrekende gegevens: 2).

We concluderen dat ernstige complicaties van ARS optreden bij een overigens gezonde populatie. Naar schatting bij 1: 12.000 gevallen van acute bacteriële rhinosinusitis in de pediatrische populatie en bij 1: 32.000 volwassenen met acute bacteriële rhinosinusitis in Nederland. Onze studie suggereert dat antibioticabehandeling voor acute rhinosinusitis in de huisartspraktijk geen rol speelt bij het voorkomen van complicaties.

In hoofdstuk 4.2 proberen we zorgverleners bewust te maken van het onnodige overmatige gebruik van antibiotica voor ARS. Om antibioticaresistentie en bijwerkingen te voorkomen, adviseren we om alleen antibiotica voor te schrijven bij patiënten met een ernstige presentatie van bacteriële ARS. Bijvoorbeeld bij patiënten met ten minste drie van de volgende ernstige symptomen: purulente afscheiding, hoge koorts, ernstige (eenzijdige) aangezichtspijn, langdurige ziekte (7 dagen of meer) en / of "dubbele ziekte" (een verslechtering na een eerdere mildere fase van ziekte). Bovendien zijn er geen gerandomiseerde gecontroleerde onderzoeken die aantonen dat zelfs bij bacteriële ARS een antibioticum nodig is. Antibiotica dienen zeker niet te worden voorschreven bij volwassenen met een ongecompliceerde ARS.

Hoofdstuk 5 – Beschouwing

We denken dat een aantal veranderingen in de dagelijkse praktijk in de eerste lijn de behandeling van rhinosinusitis kan verbeteren. Ten eerste moeten huisartsen zich bewust zijn van de verschillen tussen ARS en CRS. Om dit te ondersteunen, moet naast de reeds bestaande richtlijn over ARS een aparte richtlijn voor huisartsen (Nederlands Huisartsen Genootschap, NHG) over CRS worden ontwikkeld. Bovendien moet er een aparte code (ICD-10, International Classification of Diseases, Internationale Classificatie van Ziekten) voor beide ziekten beschikbaar zijn in registraties. We adviseren huisartsen om hun diagnose van rhinosinusitis te baseren op de symptomen die worden beschreven in EPOS. Er hoeft geen nadruk te worden gelegd op lichamelijk onderzoek in de huisartspraktijk, omdat een goed onderzoek van de middelste neusgang nauwelijks mogelijk is zonder een endoscoop. Het voorschrijven van antibiotica moet worden verminderd door de aanbevelingen in EPOS en, hopelijk in de toekomst, in de bijgewerkte NHG-richtlijnen op te volgen.

Chapter 6.3

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PhD supervisor: Prof. dr. W.J. Fokkens
PhD cosupervisor: Dr. S. Reitsma

Courses

2009 Practical biostatistics, AMC, Amsterdam, the Netherlands (ECTS 1.5)

2009 Acces: kennismaking en tabellen, AMC, Amsterdam, the Netherlands (ECTS 0.25)

2009 Acces: Query's, AMC, Amsterdam, the Netherlands (ECTS 0.25)

2010 Basis FESS course, AMC, Amsterdam, the Netherlands (ECTS 0.75)

2010 WiKiNO course, AMC, Amsterdam, the Netherlands (ECTS 0.25)

2014 Speerpuntencursus XVIII, Garderen, the Netherlands (ECTS 0.5)

2015 Medical Business Masterclass, Amsterdam, the Netherlands (ECTS 1.0)

2016 Speerpuntencursus VXIX, Garderen, the Netherlands (ECTS 0.5)

2017 Teach the teacher, AMC, Amsterdam, the Netherlands (ECTS 0.5)

2018 Speerpuntencursus VXX, Garderen, the Netherlands (ECTS 0.5)

Presentations

2009 Rhinosinusitis in de huisartsenpraktijk. Oral presentation, April 2009, KNO-vergadering, Nieuwegein, the Netherlands (ECTS 0.5)

2010 Management van rhinosinusitis in de huisartsenpraktijk. Oral presentation, April 2010, KNO-vergadering, Nieuwegein, the Netherlands (ECTS 0.5)

2011 Rhinosinusitis in General Practice. Oral presentation, 1st Congress of the Confederation of European Oto-Rhino-Laryngology, Head and Neck Surgery, June 2011, Barcelona, Spain (ECTS 1.0)

2012 Rhinosinusitis in de huisartsenpraktijk. Oral presentation, Wetenschapsdag AMC, September 2012, Amsterdam, the Netherlands (ECTS 0.5)

2014 Acute en chronische rhinosinusitis in relatie tot patiëntkarakteristieken. Oral presentation, April 2014, KNO-vergadering, Nieuwegein, the Netherlands (ECTS 0.5)

2014 Rhinosinusitis in de eerste lijn. Oral presentation, Wetenschapsdag AMC, November 2014, Amsterdam, the Netherlands (ECTS 0.5)

2015 Acute And Chronic Rhinosinusitis And Allergic Rhinitis In Relation To Environment, Comorbidity And Ethnicity. Poster presentation, 10th Symposium of Experimental Rhinology and Immunology of the Nose, SERIN March 2015, Stockholm, Sweden (ECTS 1.0)

Teaching

2008-2016 Monthly teaching of otorhinolaryngology interns, AMC, Amsterdam, the Netherlands (ECTS 4.0)

2008-2016 Twice yearly preparing and presenting Critical Appraisals of a Topic (CAT), AMC, Amsterdam, the Netherlands (ECTS 4.0)

(Inter)national conferences

2008 – 2018 Twice yearly KNO-vergadering, Nieuwegein, the Netherlands (ECTS 4.0)

2008 – 2018 Weekly attending Critical Appraisals of a Topic (CAT), AMC, Amsterdam, the Netherlands (ECTS 4.0)

2011 1st Congress of the Confederation of European Oto-Rhino-Laryngology, Head and Neck Surgery, 2011, Barcelona, Spain

2014 25th Congress of the European Rhinology Society, 2014, Amsterdam, the Netherlands (ECTS 0.5)

2015 10th Symposium of Experimental Rhinology and Immunology of the Nose, SERIN, 2015, Stockholm, Sweden

Publications

Hoffmans R, Stokroos RJ, Rikers M, Kingma H, Kremer B. Adverse patient occurrences in otorhinolaryngology: results of a systematic registry in a tertiary referral hospital. Laryngoscope. 2007 Jun;117(6):1112-7.

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