Corticosteroids
for
acute rhinosinusitis

Roderick P. Venekamp

Corticosteroids for acute rhinosinusitis

Corticosteroïden voor acute rhinosinusitis
(met een samenvatting in het Nederlands)

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Manuscripts based on the studies presented in this thesis

Chapter 1
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Chapter 2
Venekamp RP, Rovers MM, Verheij TJM, Bonten MJM, Sachs APE. Treatment of acute rhinosinusitis: discrepancy between guideline recommendations and clinical practice. *Family Practice 2012; doi: 10.1093/fampra/cms022.*

Chapter 3.1
Venekamp RP, Sachs APE, Bonten MJM, Verheij TJM, van der Heijden GJMG, Rovers MM. Intranasal corticosteroid monotherapy in acute rhinosinusitis: An evidence-based case report. *Otolaryngol. Head Neck Surg. 2010; 142(6): 783-8.*

Chapter 3.2
Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del Mar C, Perera R, Glasziou PP, Rovers MM. Systemic corticosteroids for acute sinusitis. *Cochrane Database of Systematic Reviews 2011, Issue 12. Art no.: CD008115. DOI:10.1002/14651858.CD008115.pub2.*
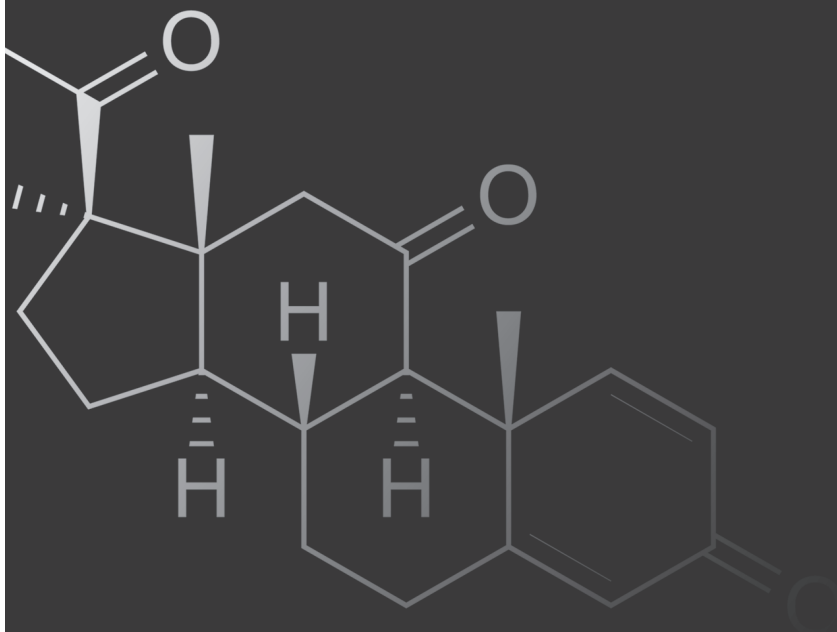
Chapter 4
Venekamp RP, Bonten MJM, Rovers MM, Verheij TJM, Sachs APE. Systemic corticosteroids for clinically diagnosed acute rhinosinusitis: a randomised controlled trial. *Submitted*

Chapter 5
Venekamp RP, Rovers MM, Hoes AW, Knol MJ. Subgroup analysis in randomised controlled trials: It is not all relative. *Submitted*

Contents

Chapter 1

General introduction

Acute rhinosinusitis

Definition, incidence, diagnosis and natural course

Pathophysiologically, acute rhinosinusitis (ARS) is defined as swelling of both the contiguous nasal and paranasal mucosa.[1][2] Nowadays, it is thought that this mucosal swelling leads to obstruction of the sinus ostium, retention of mucus and characteristic signs and symptoms of ARS, which includes nasal discharge, nasal congestion, facial pain/pressure and reduction of smell lasting for less than twelve weeks.[2] If symptoms persist for more than three months, the condition is defined as chronic rhinosinusitis (with or without nasal polyps). Since these conditions may differ from an aetiological and/or pathophysiological point of view, this thesis will focus on ARS.[2]

Almost all patients with ARS are seen and treated in general practice with incidence rates for children and adults combined in both the United Kingdom (1997)[3] and the Netherlands (2001)[4] of approximately 22 per 1000 patients annually, while sinusitis does affect one out of seven adults in the United States each year according to a national health survey.[5] Whereas ARS also occurs in children, the majority of patients who visits their GP with this condition are adults.[6][7] Nevertheless, recent data on incidence and prescription rates for ARS in adults is lacking.

In general practice, diagnosing ARS is based on clinical signs and symptoms.[2] The additional diagnostic value of laboratory measurements (e.g. C-reactive protein, erythrocyte sedimentation rate, and leukocyte count) and imaging techniques such as sinus X-ray and sinus ultrasound is too low to be implemented.[8-13] The use of more advanced and invasive diagnostic instruments, such as nasal endoscopy, computed tomography (CT) scanning and sinus puncture are not feasible in general practice. In the vast majority of patients, ARS is a self-limiting disease that subsides within one to four weeks.[14-17] Despite decongestive nose drops and pain reduction induced by analgesics, the convalescence period is long and inconvenient for most patients as this condition is associated with unpleasant symptoms such as facial pain, nasal congestion, loss of smell and/or appetite, and insomnia. These symptoms can therefore considerably impair daily functioning, are associated with a negative influence on the quality of life and might lead to absenteeism from work and/or school.[18] As a consequence, patients may seek medical attention in order to relieve symptoms and accelerate recovery.

An example from daily practice

A 42 year old female patient visits her general practitioner (GP). Her medical history is unremarkable besides obesity and laparoscopic inguinal hernia repair surgery in 2006. She quit smoking in 2005. Looking in her electronic medical record the GP sees that her last visit was approximately nine months ago when antibiotics were prescribed because of an episode of persistent cough. Now, the patient is complaining of maxillary pain, nasal discharge and blockage, reduction of smell and sleep disturbance for more than seven days. Attempting to relieve symptoms she has already started with over-the-counter decongestive nose drops and analgesics (paracetamol). Unable to perform her daily activities, she is now desperately asking her doctor to prescribe an effective drug for her complaints. Being aware of the limited role of antibiotics in this condition, the GP is wondering whether corticosteroids might be beneficial for shortening the course of the patients' symptoms.

Aetiology: bacterial infection to be treated with antibiotics?

ARS is frequently considered a bacterial infection of the paranasal sinuses, preferably to be treated with antibiotics.[2][19] However, studies have shown that only 0.5-2% of viral upper respiratory tract infections are complicated by bacterial infection.[20][21] Currently, no clinical sign, test or symptom has been identified to help the GP discriminate between viral and bacterial sinus infection. Over the years, numerous RCTs with antibiotics have been performed to assess their clinical effectiveness in adult patients with ARS in general practice.[15-17, 22-28] Although antibiotics might be beneficial in a subgroup of patients in which the diagnosis is confirmed by CT scan[29], trials on the effectiveness of antibiotics in clinically diagnosed ARS failed to demonstrate beneficial clinical effects. Moreover, a recent meta-analysis of individual patient data could not detect predictors for beneficial effects of antibiotics among common clinical signs and symptoms.[14] Despite this overwhelming evidence, physicians continue to prescribe oral antibiotics very frequently in patients with symptoms of ARS. Being the fifth most common condition for which an antibiotic is prescribed in the United States[6], antibiotic prescription rates for ARS in Europe range from 70% in the Netherlands to 92% in the United Kingdom.[3][4][30] This routine pratice is accompanied by unnecessary side effects and might lead to enhancement of antimicrobial resistance.[31-33] New treatment targets for clinically diagnosed ARS should therefore shift away from antibiotics. However, till date, no treatment strategy has proved to be effective. In a small study, (peroral) decongestive therapy appeared to have no beneficial clinical effects when added to antibiotics.[34]

Additionally, neither intranasal sodium cromoglycate[35] nor nasal irrigation with (hypertonic) saline[36] proved to be effective. Moreover, no evidence is available to support the use of non-steroidal anti-inflammatory drugs, antihistamines, mucolytics, nasal anticholinergics or steam inhalation therapy in patients with ARS.

Aetiology reconsidered: pivotal role of inflammation?

Nowadays, there is a growing tendency among experts to regard acute inflammation of the paranasal mucosa due to infectious (e.g. viruses, bacteria) and non-infectious (e.g. allergens, idiopathic triggers) causes as the predominant path in the causation of symptoms in ARS.[1 37] It is thought that the host inflammatory response leads to accumulation of inflammatory mediator cells which in turn leads to increased mucus production, (para)nasal mucosal swelling, obstruction of the ostiomeatal complex and finally the characteristic signs and symptoms of ARS (Figure 1).

Figure 1. Aetiology reconsidered: pivotal role of inflammation?
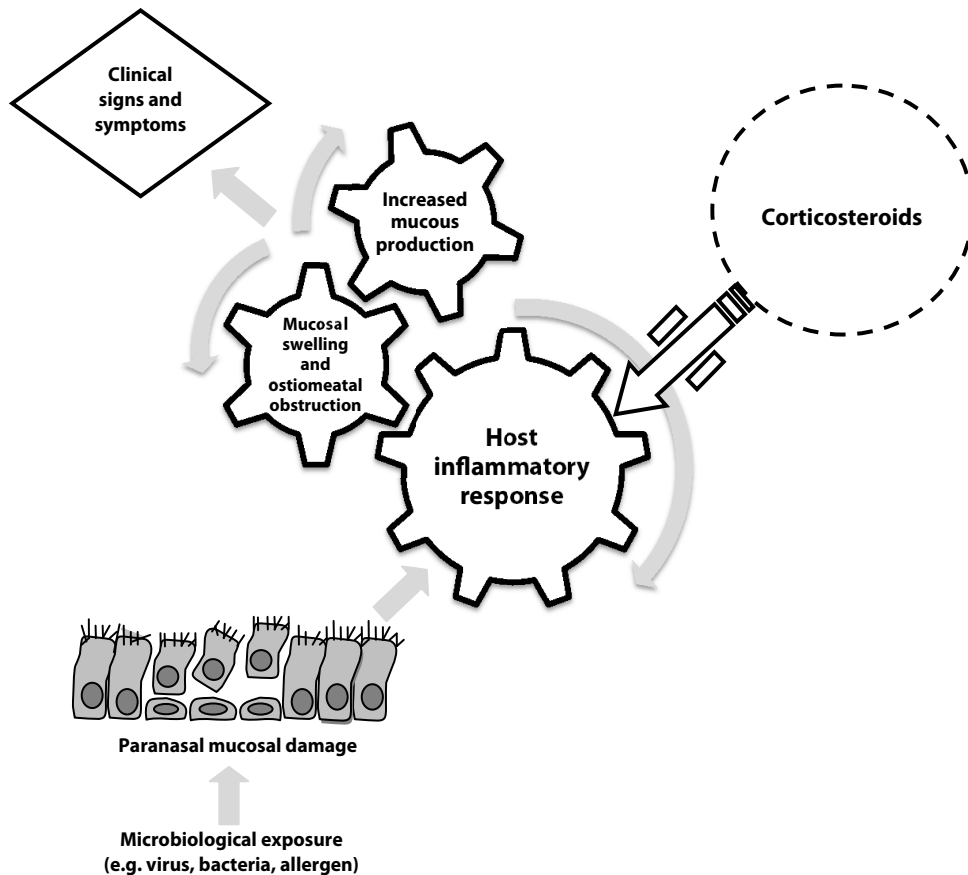
Considering ARS to be an ongoing host inflammatory response, nasal mucosal inflammation may become a more important target for treatment than antibiotics against the supposed bacterial pathogens. In line with this consideration, anti-inflammatory drugs could ameliorate the host inflammatory response and stimulate clinical improvement (Figure 1). Nevertheless, no clear scientific evidence is available to support (or reject) this hypothesis. A recent systematic review on the effectiveness of intranasal corticosteroids (INCS) with or without antibiotics in patients with ARS reported a very modest beneficial effect (for every 100 patients treated with INCS, seven additional patients had complete or marked symptom relief at 15 to 21 days; number needed to treat=15).[38] However, this review did not report a separate analysis on the effects of INCS in patients with ARS without antimicrobial co-treatment. As a consequence, the independent effect of INCS remains unknown. Moreover, an important RCT of Williamson *et al*. on the efficacy of INCS in clinically diagnosed ARS was not included in this review.[15] Furthermore, in the latter trial it was unclear whether the limited effect could be explained by the poor delivery of INCS due to blocked nasal passages or by the lack of anti-inflammatory effect in ARS.

As compared to INCS, systemic corticosteroid therapy does have several advantages such as lower costs, more convenient to use, higher corticosteroid levels and no risk of poor deliverance because of nasal blockage. Moreover, short-course systemic corticosteroid therapy has proved to be highly effective in airway diseases with a major inflammatory component, such as exacerbations of asthma and COPD[39 40] and the number of side-effects is limited and mild when short regimen (< 40 mg daily for seven to ten days) is used.[41 42] Although increasingly used in daily practice, the effectiveness of (systemic) corticosteroids for clinically diagnosed ARS is unknown.

Objectives of this thesis

The primary objective of this thesis is to evaluate the effectiveness of corticosteroids in clinically diagnosed ARS. In particular, we provide an overview of the existing evidence on the use of corticosteroids in ARS and determine the effectiveness of systemic corticosteroids by performing a double blind, placebo-controlled, randomised clinical trial.

Secondary objectives are to gain insight in daily care management for ARS over the years 2000 to 2009 and to determine which methodology is used in reporting heterogeneity of treatment effects among subgroups in RCTs.

Outline of this thesis

Chapter 2 describes the consultation and prescription rates for adult patients with ARS in general practice between 2000 and 2009. The main focus of this study is to determine whether a change in daily practice could be observed before and after the introduction of the revised guideline on ARS in 2005. In **chapter 3** we perform systematic reviews of the literature on the use of corticosteroids in ARS. We investigate the efficacy of INCS as a monotherapy (**chapter 3.1**) and the effectiveness of systemic corticosteroids (**chapter 3.2**). **Chapter 4** describes the results of a RCT to assess the effectiveness of systemic corticosteroids (prednisolone 30 mg daily for seven days) in adult patients who visited their GP with symptoms of ARS for at least five days. In **chapter 5,** we examine whether subgroup analyses were reported on a relative or absolute scale in RCTs that were published in five major general medical journals in 2010. In **chapter 6** we discuss the treatment options for clinically diagnosed ARS in a broader perspective. The thesis ends with a summary of the main findings, including recommendations for both clinical practice and future research.

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Chapter 2

Incidence and management of acute rhinosinusitis: 2000 to 2009

Abstract

Background

A revised guideline on acute rhinosinusitis (ARS) has been introduced in the Netherlands in 2005 which advocates a more judicious use of antibiotics in patients with symptoms of ARS in general practice. It is unknown whether the introduction of this revised guideline influenced daily clinical practice. Our aim therefore is to investigate whether consultation and prescription rates for ARS in adults changed over recent years in order to provide information on general practitioners' prescribing and referral behavior before and after the introduction of the revised guideline.

Methods

We performed a retrospective cohort study within the computerised database of the Utrecht General Practitioners Research Network. All patients aged 18 years or older within this database over the years 2000 to 2009 were included. Clinical diagnoses of ARS were recorded according to the International Classification of Primary Care codes (R75 and/or R09) and drug prescriptions according to the Anatomical Therapeutic Chemical classification system.

Results

ARS consultation rates for adults revealed a stable pattern, with an average consultation rate of approximately 29 episodes per 1000 person-years. From 2000 to 2005, the antibiotic prescription rate increased from 56 to 62 prescriptions per 100 episodes (p-value for time trend < 0.05). From 2005 onwards, the antibiotic prescription decreased to 56 per 100 episodes in 2009 (rate difference (RD): -6, 95% CI: -10 to -1, p-value for difference in trend between 2000-2005 and 2005-2009 < 0.05). From 2005 to 2009, the intranasal corticosteroid (INCS) prescription rate increased from 20 to 31 prescriptions per 100 episodes (RD: 11; 95% CI: 7 to 15, p-value for difference in trend between 2000-2005 and 2005-2009 < 0.01). Oral corticosteroid prescription and referral rates remained low.

Conclusion

Despite strong guideline recommendations to restrict the use of antibiotics and INCS, we found only a modest decrease in antibiotic prescription rates over recent years, whereas INCS prescription rates even increased.

Introduction

Acute rhinosinusitis (ARS) is an important reason of consultations and antibiotic prescriptions in general practice and is accompanied with high financial burden on society.[1-3] Whereas ARS also occurs in children, the vast majority of patients who visits their general practitioner (GP) with this condition are adults.[4 5] Previous studies reported a decline in consultation rates for ARS in general practice, which is in agreement with incidence patterns of other upper respiratory tract infections.[1 6 7] However, recent data on consultation rates in adults are lacking since these studies reported consultation rates of both children and adults combined over the period 1987-2001.

Symptoms consistent with ARS are self-limiting in the majority of patients within 2-4 weeks.[8] Nevertheless, ARS is the fifth most common condition for which an antibiotic is prescribed in the USA[4], while antibiotic prescription rates in Europe ranged from 70% in the Netherlands (2001) to 92% in the UK (1997).[1 2 9] Earlier studies revealed that overprescription of antibiotics might be caused by patients' misconceptions on the efficacy of antibiotics in viral infections[10] and GPs' overestimation of patients' expectations towards antibiotics.[11 12] In addition, the lack of specific knowledge about respiratory tract infections has been identified as an important reason.[13] To increase disease-specific knowledge and improve health care decisions, the Dutch College of General Practitioners developed an evidence-based guideline for management of ARS in 1993.[14] As numerous placebo-controlled trials have failed to demonstrate a clinical beneficial effect of antibiotics in clinically diagnosed ARS in the past decade, an even more restricted use of antibiotics was justified and therefore a revised guideline was issued in 2005.[15] This revised guideline advocates a more judicious use of antibiotics and emphasise that antibiotic prescriptions may only be considered in patients with (i) severe illness, (ii) fever that recurs after a fever-free period within one ARS episode, (iii) symptoms that last for more than 14 days, (iv) recurrent ARS (more than three episodes in previous year) or (v) immunodeficiency. Doxycycline and amoxicillin are considered to be the first-choice antibiotics. Besides, the guideline recommends to restrict the use of intranasal corticosteroids (INCS) to patients in which previous treatment options have failed.

Almost all GPs in the Netherlands had full access to this guideline by its publication on the open access website of the Dutch College of General Practitioners and publication in the College National Journal, i.e. Huisarts en Wetenschap (over 90% of Dutch GPs are member). In addition, GPs received an abstract of the guidelines' most important revisions and recommendations for clinical practice to further enhance implementation. Furthermore, Dutch GPs have to follow postgraduate courses including medical educational sessions in which the guidelines are discussed in order to obtain re-registration.

It is unknown whether a change in daily clinical practice could be observed after the introduction of the revised guideline in 2005. Our aim, therefore, was to investigate whether consultation and prescription rates for ARS in adults changed over recent years in order to provide information on GPs' prescribing and referral patterns before and after the introduction of a revised guideline in daily practice.

Methods

Design

We used the medical database of the University Medical Center Utrecht General Practitioners Research Network (HNU) to analyse the consultation rates, therapy and management of ARS in adults between 2000 and 2009. This database comprises well-documented information of all patients enlisted in the participating general practices, which resemble a population of approximately 40,000 patients over the years 2000 to 2009. The GPs uniformly and systematically recorded patient demographics (including date of birth and gender), medical conditions and disease episodes according to the International Classification of Primary Care (ICPC), drug prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification system and hospital referrals.[16]

Study population

All patients aged 18 years or older enlisted in the participating general practices between 2000 and 2009 were included in the study. The size of this dynamic cohort did not change significantly over time.

Outcome measures

The main outcome was clinical diagnosis of ARS defined as ICPC code R75 (sinusitis) and / or ICPC code R09 (symptoms / complaints sinuses). Episodes of chronic rhinosinusitis (ICPC code R75.2) were excluded. A new episode of ARS was documented after a rhino-sinusitis-free interval of at least 28 days. Secondary outcomes were the proportion of antibiotic (ATC code J01) and steroidal anti-inflammatory drug (INCS: ATC code R01 and oral corticosteroid: ATC code H02AB) prescriptions and referrals to an otorhinolaryngologist per 100 ARS episodes. In the HNU database a direct link between a disease episode and drug prescription or referral is missing. Drug prescriptions and referrals were therefore collected from 7 days before the start of an episode until 7 days after the end of an episode.

Statistical analysis

Annual consultation rates per 1000 person-years were calculated by dividing the number of ARS episodes by the total number of person-years in a specific year. An average consultation rate was calculated for all the years combined. We performed subgroup analysis for age (18 to 40 years and 40 years or older) and gender in order to compare consultation rates across these subgroups. We have dichotomised age to 18 to 40 years and 40 years or older because atopic constitution (e.g. allergic rhinitis, asthma) is known to affect younger patients more commonly. Consequently, prescribing patterns of GPs (i.e. prescription of antibiotics or corticosteroids) may be different between these age categories.

Antibiotic and steroidal anti-inflammatory drug prescriptions and referral rates were calculated as the number of prescriptions and referrals per 100 ARS episodes recorded by the GP. In addition, we stratified prescription rates according to age, gender and atopic constitution (defined as ICPC code R97: allergic rhinitis and/or R96: asthma and/or S87: atopic dermatitis/eczema). Trend analysis over the years 2005 to 2009 was performed by calculating rate differences (RDs) and the corresponding 95% confidence intervals (CIs). Moreover, we performed interrupted time series (ITS) analyses with segmented regression.[17] These analyses enables us to provide information on the trend over time prior to introduction of the guideline (i.e. p-value for the slope over the years 2000 to 2005), the change in level immediately after the introduction of the guideline (i.e. p-value for the immediate effect of guidelines' introduction in 2005) and the change in the slope from the time period before the introduction of the guideline and the slope of the time period after the introduction of the guideline (i.e. p-value for the difference in slope between the years 2000 to 2005 and 2005 to 2009). Important assumption of this regression analysis is the fact that the error terms associated with each observation are uncorrelated. Plotting the residuals over time for both antibiotic and INCS prescription rates revealed random patterns indicating the absence of autocorrelation. Moreover, the Durbin-Watson statistic (D-W) appeared to be between 1.5 and 2.5 (D-W for antibiotic prescription rate: 1.8 and D-W for INCS prescription rate: 2.1). For the statistical analyses SPSS version 17 (SPSS Inc., Chicago, Illinois) and Rothman's Episheet version June 11, 2008 (http://www.drugepi.info/links/downloads/episheet.xls) was used.

Results

Study population

The total size of the cohort varied from 31,938 patients in 2000 to 35,803 in 2009, with an average number of 33,352 patients. Gender and age distribution did not change substantially over time: 53% of the patients were female and 71% were aged 40 years or older.

Clinical diagnosis of acute rhinosinusitis

Between 2000 and 2009 a total of 5,839 patients had at least one episode of ARS; median age at the first episode was 47 years (interquartile range: 36-57) and approximately 63% were female. The total number of ARS episodes within the study period was 9,631.

Consultation rates

The overall consultation rates of ARS revealed a stable pattern over time, with an average consultation rate of 28.9 episodes per 1000 person-years (95% CI: 28.4 to 29.5) (Figure 1). ITS analysis revealed no significant effect of the introduction of the guideline.

The consultation rate for patients aged between 18 and 40 years demonstrated a significant decline (RD: -9.5, 95% CI: -14.0 to -4.9). The consultation was almost two times higher in females (36.3 episodes per 100 person-years; 95% CI: 35.4 to 37.2) compared to males (20.8 episodes per 100 person-years; 95% CI: 20.1 to 21.5).

Antibiotic prescriptions

Before the introduction of the revised guideline, the antibiotic prescription rate revealed a statistical significant increase: from 56 prescriptions per 100 ARS episodes (95% CI: 53 to 59) in 2000 to 62 per 100 episodes (95% CI: 59 to 65) in 2005 (RD: 6; 95% CI: 1 to 10, p-value for slope in ITS analysis < 0.05) (Figure 1). From 2005 onwards, the antibiotic prescription rate decreased to 56 per 100 episodes (95% CI: 53 to 59) in 2009 (RD: -6; 95% CI: -1 to -10). The slope between the years 2000 to 2005 and 2005 to 2009 revealed a statistical significant difference (p < 0.05). The largest decrease was seen in the subgroup of atopic patients (Table 1). The type of antibiotic prescribed did not change substantially over time. Doxycycline was prescribed most frequently (±70% of the episodes in which antibiotics were prescribed), followed by amoxicillin and macrolides (±10%).

Steroidal anti-inflammatory drug prescriptions

From 2000 to 2005, the INCS prescription rate demonstrated a non-statistical significant increase: from 16 prescriptions per 100 ARS episodes (95% CI: 14 to 19) to 20 per 100 episodes (95% CI: 18 to 23) (p-value for slope in ITS analysis = 0.11). After the introduction of the guideline, the INCS prescription rate increased significantly to 31 per 100 episodes (95% CI: 28 to 34) in 2009 (RD: 11; 95% CI: 7 to 15). The slope between the years 2000 to 2005 and 2005 to 2009 demonstrated a statistical significant difference (p < 0.01). Subgroup analysis revealed similar trends (Table 1). Atopic patients received INCS more frequently compared to non-atopic patients. Over time, fluticasone was prescribed most frequently (60%-70% of the episodes in which INCS were prescribed), followed by beclometasone and mometasone (±10%-20%).

The oral steroid (OS) prescription rate was low and demonstrated a minor increase over time (RD: 1; 95% CI: 0 to 2) (Table 1). The prescription rate was similar across the different subgroups.

Referral rates

The referral rates to otorhinolaryngologists for ARS revealed a stable pattern over time with an average referral rate of 2 per 100 episodes (95% CI: 1 to 2) (Table 1). ITS analysis demonstrated no significant effect of the introduction of the guideline. No differences were found across the different subgroups.

Table 1. Consultation and prescription rates for acute rhinosinusitis in general practice *

	Rate in 2000 (95% CI)	Rate in 2005 (95% CI)	Rate in 2009 (95% CI)	Difference 2005-2009 (95% CI)
Consultation rate	**30.8 (28.9 – 29.7)**	**30.1 (28.3 – 32.0)**	**28.2 (26.5 – 30.0)**	**- 1.9 (-4.5 to 0.7)**
Age 18-40 years	35.1 (31.5–38.9)	30.9 (27.5–34.6)	21.4 (18.8–24.4)	- 9.5 (-14.0 to -4.9)
Age > 40 years	28.1 (26.7–31.2)	29.8 (27.6–32.1)	30.9 (28.8–33.2)	+ 1.2 (-1.9 to 4.2)
Male	21.9 (19.6–24.3)	20.4 (18.3–22.7)	18.7 (16.7–20.8)	-1.7 (-4.8 to 1.3)
Female	38.8 (35.9–41.8)	38.9 (36.0–41.9)	36.8 (34.1–39.6)	-2.1 (-6.1 to 1.9)
Antibiotic prescription rate	**56 (53 – 59)**	**62 (59 – 65)**	**56 (53 – 59)**	**- 6 (-10 to -1)**
Age 18-40 years	61 (56–66)	67 (62–72)	58 (52–65)	- 9 (-17 to 1)
Age > 40 years	53 (50–57)	59 (56–63)	56 (52–59)	- 3 (-9 to 1)
Male	57 (51–62)	59 (53–64)	56 (51–62)	- 3 (-1 to 5)
Female	56 (52–60)	63 (59–67)	56 (52–60)	- 7 (-12 –to -2)
Atopic	55 (47–62)	61 (55–67)	49 (44–54)	- 12 (-20 to 5)
Non-atopic	56 (52–60)	63 (59–67)	56 (52–60)	- 1 (-6 to 4)
INCS prescription rate	**16 (14 – 19)**	**20 (18 – 23)**	**31 (28 – 34)**	**+ 11 (7 to 15)**
Age 18-40 years	16 (12–20)	18 (14–23)	17 (13–23)	- 1 (-7 to 5)
Age > 40 years	17 (14–20)	21 (18–24)	35 (32–38)	+ 14 (9 to 18)
Male	14 (11–18)	19 (15–24)	32 (27–37)	+ 13 (6 to 20)
Female	17 (15–20)	21 (18–24)	31 (27–34)	+ 10 (5 to 15)
Atopic	20 (15–26)	22 (18–22)	38 (33–43)	+ 16 (18 to 23)
Non-atopic	16 (13–18)	19 (17–22)	27 (24–30)	+ 8 (3 to 12)
Oral steroid prescription rate	**1 (1 – 2)**	**2 (1 – 3)**	**3 (2 – 3)**	**+ 1 (0 to 2)**
Referral rate	**2 (1 – 3)**	**2 (2 – 3)**	**2 (2 – 3)**	**0 (-1 to 1)**

* Consultation rate per 1000 person-years; prescription rate per 100 episodes

Figure 1. Consultation (per 1000 person-years) and prescription rates (per 100 episodes) for acute rhinosinusitis in general practice
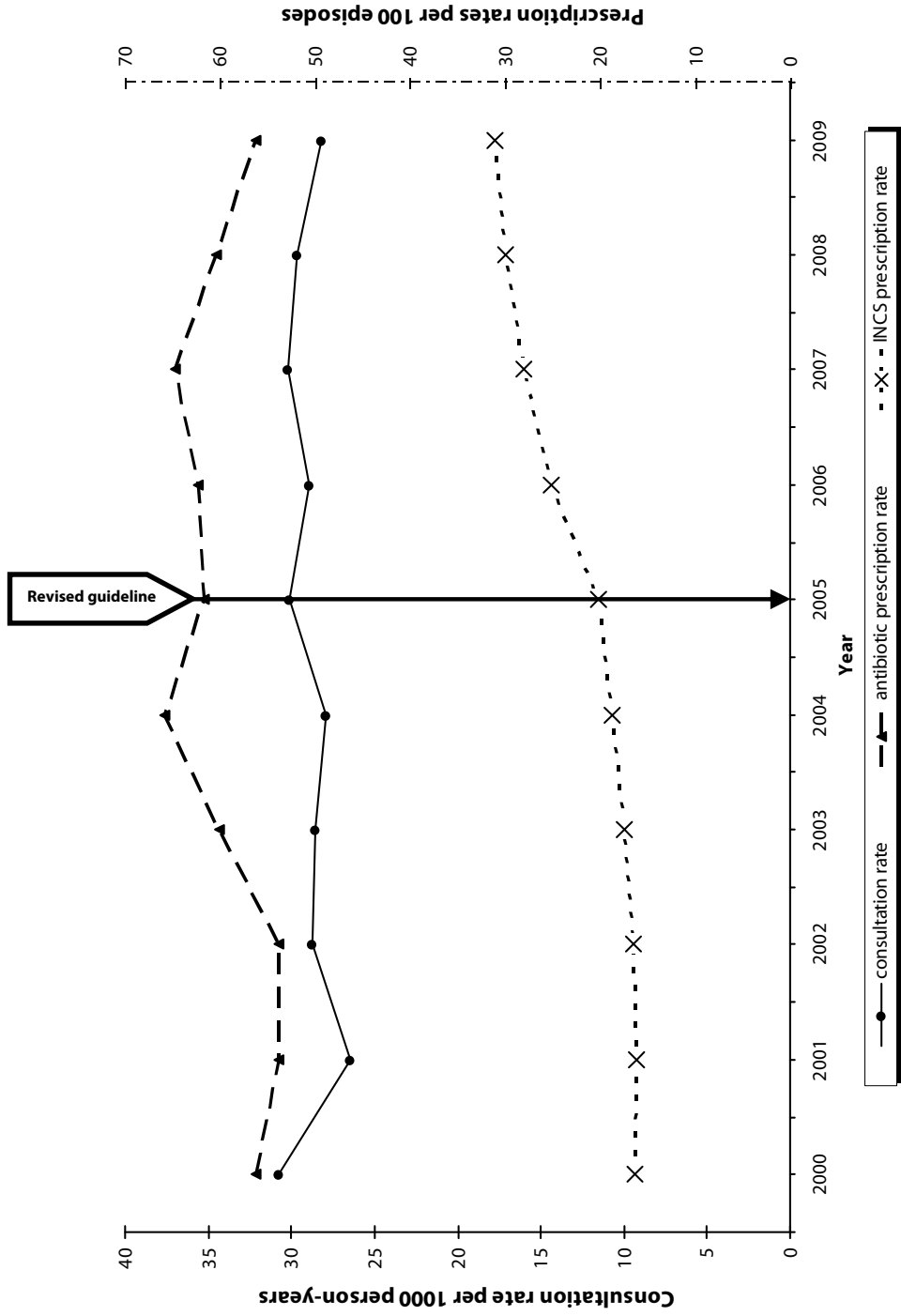
Discussion

Summary of main findings

From 2000 to 2009, ARS consultation rates for adults in general practice revealed a stable pattern with an average consultation rate of approximately 29 episodes per 1000 person-years. Consultation rates were almost two times higher in females compared to males. From 2005 onwards, we found only a modest decrease in antibiotic prescription rates, whereas INCS prescription rates even increased over this time period.

Strengths

In general practice, ARS is based on clinical signs and symptoms which includes nasal discharge, nasal congestion, reduction/loss of smell, and facial pain/pressure lasting for a maximum of 12 weeks.[15] [18] Additional diagnostic tools such as laboratory, micro-biological and imaging tests are not routinely performed in this setting prior to treatment decision. The clinical definition of ARS used in our main analysis (ICPC code R09 (symptoms /complaints sinuses) and R75 (sinusitis)) is therefore in agreement with daily practice. A previous study, however, defined ARS as ICPC code R75 (sinusitis).[1] To enhance comparability, we performed sensitivity analysis in which we restricted our outcome definition to ICPC code R75. The observed consultation rates did not change substantially over time, which is in agreement with the findings in our main analysis (ICPC code R75 and/or R09). Furthermore, the antibiotic prescription rates in this analysis resembled the prescription rates of our main analysis (i.e. 60 prescriptions per 100 episodes (95% CI: 59 to 61) with a slight decrease over recent years).

Other major strengths of our study are the size of the cohort and the quality of the data. The medical database of the University Medical Center Utrecht General Practitioners Research (HNU) comprises well documented information of enlisted patients over the years 2000 to 2009. Characteristics of these patients did not differ from the overall Dutch population and main characteristics of the GPs were comparable with total Dutch GPs with respect to age, gender, part-time and full-time workers and practice in both urban and rural areas.[19] [20] In addition, all participating GPs received continuing education regarding the correct coding of diagnostic information according to the ICPC coding system and more than 90% of the contacts did receive an ICPC code.

Limitations

Next to strengths also some potential limitations should be discussed before drawing conclusions from our findings. Firstly, the main limitation of using a medical database for research purposes is the fact that no additional information is available on the specific clinical features of patients with an episode of ARS such as duration of symptoms prior to

consultation and (the absence of) fever. As a consequence, we were not able to determine to what extend the observed antibiotic prescriptions from 2005 onwards were justified according to the revised guideline or not. However, an earlier study of Akkerman *et al.*[11] revealed that more than 20% of the antibiotic prescriptions for ARS over the years 2002 and 2003 were not in agreement with the previous ARS guideline. Given the stable consultation rates reported in our study and the strong recommendation in the revised guideline to limit the use of antibiotics in ARS, a firm decline in antibiotic prescription rates over recent years was expected when GPs would apply its recommendations into daily practice.

Secondly, other determinants than the introduction of the revised guideline in 2005 may have modified the prescription rates over time such as access to point-of-care C-reactive protein (CRP) tests, pharmaceutical pressure to prescribe INCS and a change in patients' expectations, knowledge and consultation behavior. It is, however, unlikely that these determinants have had a major influence on our results. Point-of-care CRP testing is not used by GPs in the Netherlands. Additionally, the influence of pharmaceutical pressure is likely to be limited as participating general practices did not receive pharmaceutical sales representatives. Furthermore, no public campaigns to increase patients' knowledge on the efficacy of antibiotics in ARS were held during the study period and consultation rates remained stable over time.

Thirdly, the fact that episodes and prescriptions had to be linked to each other could be criticised. However, this procedure is inherent to database research. Moreover, we excluded prescriptions clearly prescribed for other indications (i.e. antibiotics clearly prescribed for urinary tract infections) to increase accuracy of the results.

Finally, misclassification due to missing data and differences in classification between the years and GPs cannot be ruled out, and this may have resulted in either an over-estimation or underestimation of the true consultation rates. It is, however, unlikely that misclassification has affected the results substantially because over 90% of the patient contacts were coded and all participating family physicians received training regarding the correct coding.

Comparison with existing literature and clinical implications

A previous study on consultation and prescription rates for upper respiratory tract infections in general practice revealed a significant decline in consultation rates and total antibiotic prescriptions for ARS after the introduction of the guideline on ARS in 1993.[1] Nevertheless, overprescription of antibiotics remained substantial.[11] Results of our study suggest that dissemination of a revised guideline as added to medical education regarding guidelines' recommendations for a more judicious use of antibiotics did not lead to a further decline in overall consultation and antibiotic prescription rates for ARS.

In patients aged below 40 years, the consultation rate for ARS declined substantially over time. This might be explained by family physicians' response to the guidelines to consider alternative diagnoses such as (non)allergic rhinitis in younger patients with symptoms of ARS. Subsequently, family physicians may find it hard to refrain from prescribing antibiotics once ARS is diagnosed in these patients.

Our main findings are in agreement with data on total antibiotic use in the Netherlands over the past decade (http://app.esac.ua.ac.be/public) and may reflect the fact that it is difficult for family physicians to go under the current level of antibiotic prescription rates in the Netherlands, even though that rate still represents a substantial overuse. It could well be that the current Dutch level of antibiotic use for a troublesome infection like ARS is difficult to improve further due to pressure of patients and the inclination of physicians to do something, even when this is not evidence-based. A previous trial on antibiotics demonstrated beneficial effects in ARS patients in which the diagnosis is confirmed by the presence of air-fluid level or total opacification on computed tomography scanning.[21] As a consequence, there may be a subgroup among clinically diagnosed ARS patients who do benefit from antibiotics. Unfortunately, such subgroups could not be identified by a recent meta-analysis of individual patient data.[8] Until such subgroups have been identified, antibiotics should only be considered in patients with a complicated course of ARS.

To further rationalise antibiotic use, additional tools are perhaps needed to help GPs and their patients to rationalise antibiotic use. Cals *et al.*[22] recently demonstrated that the use of a near patient test and specific communication training could reduce antibiotic use for lower respiratory tract infections still substantially, even in a low prescribing country like the Netherlands. In addition, current evidence reveals that also local circumstances, like organisation of health care and patients' expectations play a pivotal role when trying to rationalise the use of medical treatment.[23] Nowadays, it is however unknown which combination of interventions lead to the highest and sustainable reduction of antibiotic prescriptions in daily practice.[24] Currently therefore, our research group is collaborating in both national and international research projects to determine and evaluate the most effective strategy in different settings.

Next to increasing GPs' awareness on a more appropriate prescribing behavior, public beliefs towards antibiotics may also be an important target for intervention in order to reduce unnecessary prescriptions. Increasing patients' knowledge on the ineffectiveness of antibiotics in clinically diagnosed ARS by patient educational materials and public campaigns might reduce consultation rates and, subsequently, antibiotic prescriptions in daily clinical practice.

Conclusions
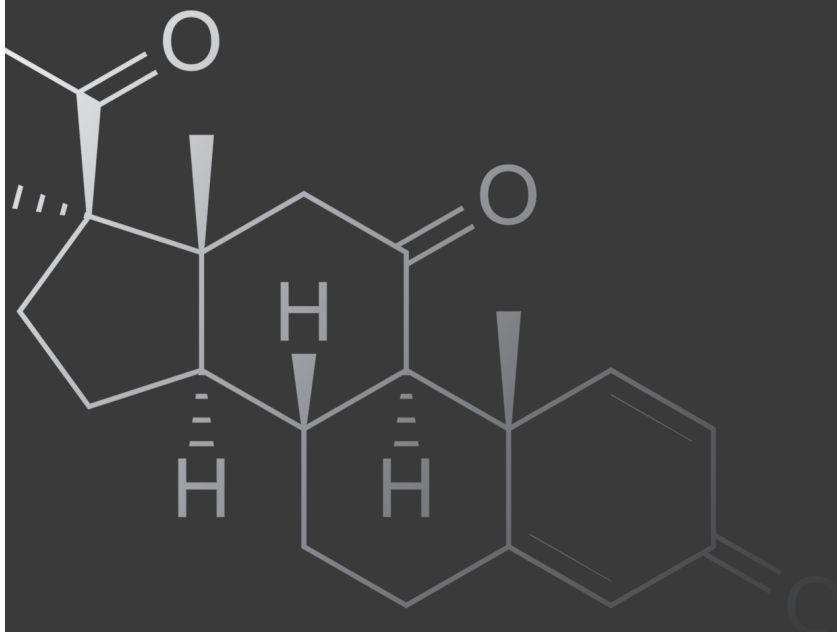
This study reports a stable pattern of consultation rates for ARS over the period 2000 to 2009. Moreover, we found only a modest decrease in antibiotic prescription rates over recent years, whereas INCS prescription rates even increased. This daily practice is not in agreement with recommendations of the revised ARS guideline to restrict the use of antibiotics and INCS in this condition.

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Chapter 3

Systematic reviews of the literature
on the use of corticosteroids
in acute rhinosinusitis

Chapter 3.1

Intranasal corticosteroid monotherapy for acute rhinosinusitis

Abstract

Background

Despite overwhelming evidence on their limited effectiveness, physicians continue to prescribe oral antibiotics very frequently in patients with symptoms of acute rhinosinusitis (ARS). New treatment targets for ARS should therefore shift away from antibiotics. Nowadays, it is thought that anti-inflammatory drugs could be effective in ARS. As a consequence, intranasal corticosteroid (INCS) monotherapy might be a potential treatment option. In this review we studied the clinical question: Does INCS monotherapy reduce time to recovery in adults with ARS?

Methods

A literature search in PubMed, Embase.com, Cochrane Library and Cinahl-Ovid was performed to identify studies on the effectiveness of INCS as a monotherapy in patients with ARS. We systematically assessed the methodological quality of the included studies and extracted data.

Results

The search yielded 490 papers of which only 2 were relevant and had a high validity regarding our clinical question. Williamson *et al.*, who used a factorial designed RCT, did neither report a difference in the proportion of clinically cured patients at Day 10 (absolute risk difference: 0% (95% CI: -12.6% to 12.7%)) nor in the Total Symptom Score at Day 10. Another large RCT, performed by Meltzer *et al.*, reported a statistically significant difference in mean Major Symptom Scores (MSS) over the 15-day treatment period within both INCS groups (once and twice daily) as compared to the placebo group. However, the clinical relevance of mean MSS as primary endpoint is debatable and the size of the reported effect in this study is modest.

Conclusion

Current evidence demonstrates that the clinical beneficial effect of INCS monotherapy compared to placebo has not been established in patients with ARS.

Case history

A 33 year old female patient visits your practice. She is complaining of fatigue, nasal discharge and obstruction, hyposmia and facial (maxillary) pain. These symptoms started some ten days ago and during the first days she had mild fever. Unable to work, she is now wondering whether she could benefit from intranasal corticosteroids (INCS) because she read on the internet that INCS are beneficial in acute rhinosinusitis (ARS). Since you are not sure about the evidence of prescribing these agents for this condition you decide to evaluate the existing literature.

Introduction

ARS is a common reason to consult a doctor and is accompanied with high direct and indirect health care costs.[1-3] Although ARS is self-limiting in the majority of adults within one to four weeks, its unpleasant symptoms can considerably impair daily functioning and may have a negative influence on the quality of life.[4] As most episodes of ARS are caused by viruses, the vast majority of patients do not benefit from antibiotics.[5] Despite overwhelming evidence, physicians continue to prescribe oral antibiotics very frequently[1 2 6], which may lead to unnecessary side effects and enhancement of anti-microbial resistance.[7-9] In order to accelerate recovery and reduce antimicrobial resistance, treatment targets for ARS should shift away from antibiotics.

Nowadays, it is thought that nasal mucosal inflammation is a more important target for treatment than possible microbiological pathogens.[10-12] Consequently, anti-inflamma-tory drugs could be effective by reducing the inflammatory response and enhancing clearance of the sinuses. INCS have proved to be effective in controlling seasonal and perennial allergic rhinitis symptoms by reducing sinonasal mucosal inflammation[13 14] and are well-tolerated and safe.[15 16] INCS monotherapy might therefore be a potential treatment option to shorten the duration of ARS.

In this review we studied the clinical question: Does INCS monotherapy reduce time to recovery in adults with ARS?
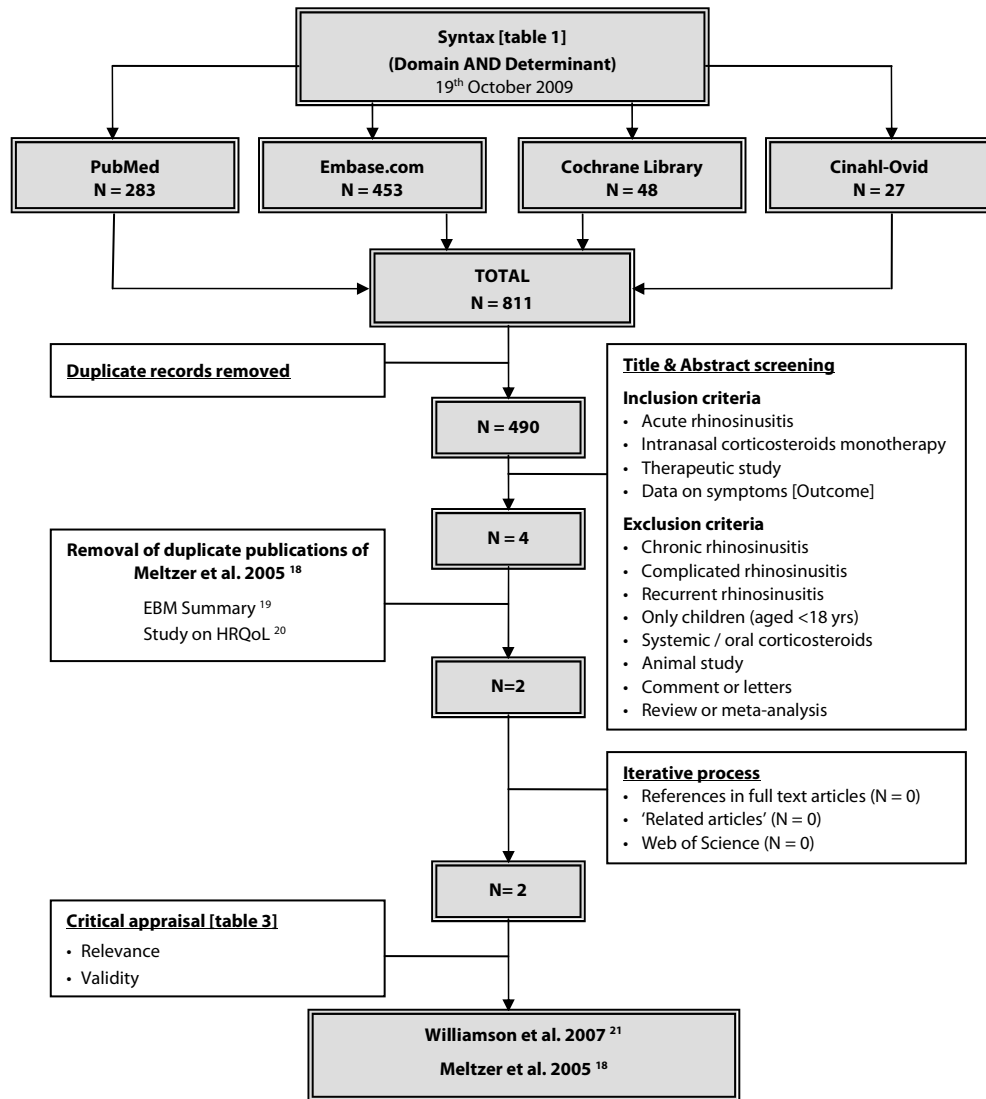
Methods

We designed a search filter using relevant synonyms for the domain, being adults with ARS, and the determinant, which is INCS treatment. ARS was defined as inflammation of

the (para)nasal mucosa characterised by both nasal (e.g. obstruction, discharge) and sinus (facial pain/pressure, tooth pain) complaints lasting for a maximum of twelve weeks.[17]

We retrieved relevant publications in PubMed, Embase.com, Cochrane Library and Cinahl-Ovid using search terms in title and abstract fields. Our search yielded 283 records in PubMed, 453 articles in Embase.com, 48 in Cochrane Library and 27 in Cinahl-Ovid (Box 1). Title and abstract of all retrieved records were screened using the following inclusion criteria: 'adult patients (aged ≥ 18 years) with ARS', 'INCS monotherapy', and 'therapeutic study'. The exclusion criteria are shown in the flowchart (Figure 1). Upon screening, 4 publications remained for further analysis. The full-text of the 4 selected publications was studied in more detail for their relevance in terms of our domain, determinant and outcome. As a result, 2 publications were excluded (Figure 1). These studies appeared to be duplicate publications of the main study by Meltzer *et al.*[18], i.e. one was an EBM summary[19] and the other publication[20] reported the effects on health-related quality of life (HRQoL).

Box 1. Search strategy

Database	Search (performed 19th October 2009)	Hits
PubMed	("sinusitis"[tiab] OR "rhinosinusitis"[tiab] OR ("sinus"[tiab] AND ("infection"[tiab] OR "inflammation"[tiab]))) AND (("Corticosteroid"[tiab] OR "Corticosteroids"[tiab] OR "Steroid"[tiab] OR "Steroids"[tiab] OR "Corticoid"[tiab] OR "Corticoids"[tiab] OR "Glucocorticoid"[tiab] OR "Glucocorticoids"[tiab] OR "Glucocorticosteroid"[tiab] OR "Glucocorticosteroids"[tiab] OR "Beclomethason"[tiab] OR "Beclometason" [tiab] OR "Beclomethasone"[tiab] OR "Beclometasone" [tiab] OR "Betamethason"[tiab] OR "Betametason" [tiab] OR "Betamethasone"[tiab] OR "Betametasone" [tiab] OR "Fluticason"[tiab] OR "Fluticasone"[tiab] OR "Budesonide"[tiab] OR "Mometasone"[tiab]) AND ("Intranasal"[tiab] OR "Intra-nasal"[tiab] OR "Intranasally"[tiab] OR "Intra-nasally"[tiab] OR "Topical"[tiab] OR "Spray"[tiab]))	**283**
Embase.com	('sinusitis' OR 'rhinosinusitis' OR ('sinus' AND ('infection' OR 'inflammation'))) AND (('corticosteroid' OR 'corticosteroids' OR 'steroid' OR 'steroids' OR 'corticoid' OR 'corticoids' OR 'glucocorticoid' OR 'glucocorticoids' OR 'glucocorticosteroid' OR 'glucocorticosteroids' OR 'beclomethason' OR 'beclometason' OR 'beclomethasone' OR 'beclometasone' OR 'betamethason' OR 'betametason' OR 'betamethasone' OR 'betametasone' OR 'fluticason' OR 'fluticasone' OR 'budesonide' OR 'mometasone') AND ('intranasal' OR 'intra-nasal' OR 'intranasally' OR 'intra-nasally' OR 'topical' OR 'spray')):ti:ab	**453**
Cochrane Library	('sinusitis' OR 'rhinosinusitis' OR ('sinus' AND ('infection' OR 'inflammation'))) AND (('corticosteroid' OR 'corticosteroids' OR 'steroid' OR 'steroids' OR 'corticoid' OR 'corticoids' OR 'glucocorticoid' OR 'glucocorticoids' OR 'glucocorticosteroid' OR 'glucocorticosteroids' OR 'beclomethason' OR 'beclometason' OR 'beclomethasone' OR 'betamethason' OR 'betamethasone' OR 'beclometason' OR 'beclometasone' OR 'betametason' OR 'betametasone' OR 'fluticason' OR 'fluticasone' OR 'budesonide' OR 'mometasone') AND ('intranasal' OR 'intra-nasal' OR 'intranasally' OR 'intra-nasally' OR 'topical' OR 'spray'))	**48**
Cinahl-Ovid	TI (('sinusitis' OR 'rhinosinusitis' OR ('sinus' AND ('infection' OR 'inflammation'))) AND (('corticosteroid' OR 'corticosteroids' OR 'steroid' OR 'steroids' OR 'corticoid' OR 'corticoids' OR 'glucocorticoid' OR 'glucocorticoids' OR 'glucocorticosteroid' OR 'glucocorticosteroids' OR 'beclomethason' OR 'beclomethasone' OR 'betamethason' OR 'betamethasone' OR 'beclometason' OR 'beclometasone' OR 'betametason' OR 'betametasone' OR 'fluticason' OR 'fluticasone' OR 'budesonide' OR 'mometasone') AND ('intranasal' OR 'intra-nasal' OR 'intranasally' OR 'intra-nasally' OR 'topical' OR 'spray'))) or AB (('sinusitis' OR 'rhinosinusitis' OR ('sinus' AND ('infection' OR 'inflammation'))) AND (('corticosteroid' OR 'corticosteroids' OR 'steroid' OR 'steroids' OR 'corticoid' OR 'corticoids' OR 'glucocorticoid' OR 'glucocorticoids' OR 'glucocorticosteroid' OR 'glucocorticosteroids' OR 'beclomethason' OR 'beclomethasone' OR 'betamethason' OR 'betamethasone' OR 'beclometason' OR 'beclometasone' OR 'betametason' OR 'betametasone' 'fluticason' OR 'fluticasone' OR 'budesonide' OR 'mometasone') AND ('intranasal' OR 'intra-nasal' OR 'intranasally' OR 'intra-nasally' OR 'topical' OR 'spray')))	**27**

Figure 1. Flowchart

Syntax [table 1]
(Domain AND Determinant)
19th October 2009

PubMed
N = 283

Embase.com
N = 453

Cochrane Library
N = 48

Cinahl-Ovid
N = 27

TOTAL
N = 811

Duplicate records removed

N = 490

Title & Abstract screening

Inclusion criteria
- Acute rhinosinusitis
- Intranasal corticosteroids monotherapy
- Therapeutic study
- Data on symptoms [Outcome]

N = 4

Exclusion criteria
- Chronic rhinosinusitis
- Complicated rhinosinusitis
- Recurrent rhinosinusitis
- Only children (aged <18 yrs)
- Systemic / oral corticosteroids
- Animal study
- Comment or letters
- Review or meta-analysis

Removal of duplicate publications of
Meltzer et al. 2005 [18]

EBM Summary [19]
Study on HRQoL [20]

N=2

N= 2

Iterative process
- References in full text articles (N = 0)
- 'Related articles' (N = 0)
- Web of Science (N = 0)

Critical appraisal [table 3]
- Relevance
- Validity

Williamson et al. 2007 [21]

Meltzer et al. 2005 [18]

The quality of methods and reporting of results of the remaining two articles were critically appraised, using the criteria shown in Table 1. The publications of Williamson *et al.*[21] and Meltzer *et al.*[18] were of adequate quality. Williamson *et al.*[21] provided numerical data on symptom resolution over time that allowed us to calculate the absolute risk difference (aRD) and corresponding confidence interval. Unfortunately, Meltzer *et al.*[18] did neither provide numerical data on symptom resolution over time nor standard deviations. Therefore, confidence intervals for the mean differences in their Major Symptom Scores (MSS) could not be calculated.

Results

Williamson *et al.*[21] performed a double-blind, double-dummy, randomised, placebo-controlled factorial trial to assess the effectiveness of amoxicillin and budesonide (200 μg once daily) in 240 patients aged 16 years or older with acute maxillary sinusitis. Acute maxillary sinusitis was defined as non-recurrent illness (< 28 days) and a minimum of 2 of the Berg and Carenfelt criteria.[22] They demonstrated that the proportion of patients with resolution of symptoms at Day 10 did not differ between budesonide and no budesonide: both 68.6%, aRD: 0% (95% CI: -12.6% to 12.7%) (Table 2). Besides, there was no difference in median Total Symptom Score (TSS) at day 10 between both groups.

Meltzer *et al.*[18] performed a double-blind, double-dummy, randomised, placebo-controlled trial to evaluate the efficacy of mometasone furoate nasal spray (MFNS) monotherapy (200 μg once daily and 200 μg twice daily) versus amoxicillin and placebo in 981 patients (≤ 12 years) with signs and symptoms of ARS. ARS was defined as uncomplicated illness (≥ 7 days but ≤ 28 days) with a low Major Symptom Score (MSS ≥ 5 but ≤ 12) and no more than 3 of the 5 symptoms rated as severe. Moreover, patients were excluded if they had signs and symptoms of fulminant bacterial rhinosinusitis. The study revealed that MFNS 200 μg twice daily led to a 9% relative improvement in mean MSS over day 2-15 compared to placebo (3.80 versus 4.61; absolute difference in mean MSS: 0.81, p<0.001) (Table 2). MFNS 200 μg once daily was also statistically significantly superior to placebo, but the effect was smaller than MFNS 200 μg twice daily (absolute difference in mean MSS: 0.45, p=0.018).

Table 1. Critical Appraisal

	Study design	Domain	Relevance / Determinant	Outcome	Concealment of allocation	Standardisation	Missing data (%)	Intention-to-treat analysis	Level of evidence
Williamson et al. (2007)	RCT Double-blind Double-dummy Factorial N = 240	Adults (≥ 16 yrs) with acute non-recurrent sinusitis	1. Amoxicillin 500 mg TID, placebo INCS 2. Placebo AB, budesonide 200 µg each nostril QD 3. Amoxicillin 500 mg TID, budesonide 200 µg each nostril QD 4. Placebo AB, placebo INCS	Proportion of patients cured at Day 10 Difference in median TSS at Day 10	+	+	13.7% (n=33)	+	1b
Meltzer et al. (2005)	RCT Double-blind Double-dummy N = 981	Patients (≥ 12 yrs) with acute non-recurrent rhinosinusitis	1. Amoxicillin 500 mg TID, placebo INCS 2. Placebo AB, MFNS 200 µg each nostril QD 3. Placebo AB, MFNS 200 µg each nostril BID 4. Placebo AB, placebo INCS	Mean MSS	?	+	9.8% (n=96)	+	1b

Legend
+ Good; +/- Moderate; – Poor ; ? Unknown; MSS, Major Symptom Score; TSS, Total Symptom Score; AM/PM, Ante Meridiam/Post Meridiam; QD, Once daily; BID, Twice daily; TID, Three daily

45

Table 2. Results

Williamson *et al.* (2007)	Budesonide 200 µg qd (95% CI)	No budesonide (95% CI)		Absolute Risk Difference (95% CI)
Proportions of patients clinically cured at Day 10	70 / 102 68.6% (59.6-77.6)	72 / 105 68.6% (59.7-77.5)		0% (-12.6 to 12.7)
Difference in median TSS at day 10 (95% CI)	0 (-0.70 to 0.70)			
Meltzer *et al.* (2005)	MFNS 200 µg qd	MFNS 200 µg bid	Placebo	
Mean MSS over day 2-15	4.16	3.80	4.61	
Difference in mean MSS with placebo (p–value)	0.45 (p=0.018)	0.81 (p<0.001)	ref	

Legend

qd, once daily; TSS, total symptom score; MFNS, mometasone furoate nasal spray; bid, twice daily; MSS, major symptom score; ref, reference group

Total Symptom Score (range 0-66) = sum of scores for (1) nasal blockage on the left side, (2) nasal blockage on the right side, (3) discharge from the nose (left nostil), (4) discharge from the nose (right nostril), (5) unpleasant taste or smell, (6) pain in the face on the left side, (7) pain in the face on right side, (8) pain in the head, jaws, teeth on bending, (9) level of restriction on daily activity, (10) level of wellness, and (11) headache

Major Symptom Score (range 0-12) = sum of scores for (1) rhinorrhea, (2) postnasal drip, (3) nasal congestion/stuffiness, (4) sinus headache and (5) facial pain/pressure/tenderness on palpation over the paranasal sinuses

Discussion

Before translating the evidence into practice, there are several potential limitations which deserve further discussion. Firstly, Williamson *et al.*[21] used a factorial design, which is the most efficient design for testing more than one hypothesis. Such a design requires, however, a specific data-analysis method with assessment for treatment interactions which results in loss of statistical power to detect differences between treatment groups. Since the confidence intervals around the reported measures of association are relatively small, we do not consider this as a drawback.

Secondly, Meltzer *et al.*[18] did not report concealment of allocation. Consequently, the risk of bias cannot entirely be excluded. Moreover, the primary endpoint (i.e. mean MSS over day 2-15) used by Meltzer *et al.*[18] can be criticised from a clinical point of view. Although methodological correct, the presented outcome does not provide information on the absolute effect of INCS. It therefore would have been clinically more informative if the absolute numbers of patients with symptom resolution at Day 15 for the treatment groups were presented. Furthermore, the size of the reported effect in this study is too modest to exceed the threshold for clinical importance.

Thirdly, the differences in study population between the two critically appraised studies may have had important impact on the results. Williamson *et al.*[21] included patients with a minimum of 2 Berg and Carenfelt criteria[22] (purulent nasal discharge with unilateral predominance, local pain with unilateral predominance, purulent nasal discharge bilaterally and pus on inspection inside the nose). These criteria have been suggested to increase the likelihood of an underlying bacterial infection, and antibiotics might therefore be more effective than INCS. However, neither antibiotic nor INCS treatment was found to be effective. As opposite to Williamson *et al.*[21], patients included by Meltzer *et al.*[18] had less severe symptoms and a reduced likelihood of a bacterial infection. As a consequence, these patients were more likely to benefit from INCS rather than antibiotic treatment. However, the differences between both INCS groups and the placebo group reported by Meltzer *et al.*[18] are modest.

Finally, one can argue on the dosage of INCS used in both trials. Williamson *et al.*[21] used INCS 200 μg once daily in both nostrils, while Meltzer *et al.*[18] revealed that INCS twice daily 200 μg had a larger treatment effect. Moreover, patients in both studies did not use decongestive nose drops before application of INCS which might have lead to a suboptimal treatment effect. Therefore, additional large randomised, placebo-controlled trials on the efficacy of higher dosages (intranasal) corticosteroids, in addition to decongestive nose drops, are warranted to provide a more definite answer on the use of this therapy in patients with ARS.

Conclusion and recommendation

As the clinical beneficial effect of intranasal corticosteroids monotherapy compared to placebo has not been established in patients with acute rhinosinusitis, watchful waiting in our female patient appears to be justified.

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Chapter 3.2

Systemic corticosteroids for acute rhinosinusitis

A systematic review

Abstract

Background

Acute rhinosinusitis (ARS) is a common reason for patients to seek medical attention. Corticosteroids might have beneficial effects in this condition. However, studies on intranasal corticosteroids (INCS) reported no or only modest beneficial effects. Systemic administration of corticosteroids may allow more effective delivery of corticosteroids to the paranasal mucosa than INCS, providing increased anti-inflammatory effects. The objective of this systematic review was therefore to assess the efficacy of systemic corticosteroids in relieving symptoms of ARS.

Methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2 2011, MEDLINE (1966 to June week 2, 2011) and EMBASE (January 2009 to June 2011) for randomised controlled trials (RCTs) comparing systemic corticosteroids to placebo or standard clinical care for ARS. Two review authors independently assessed methodological quality of the trials and extracted data.

Results

Four RCTs with a total of 1008 adult participants met our inclusion criteria. We judged studies to be of moderate methodological quality. ARS was defined clinically in all trials. However, the three trials performed in ear, nose and throat outpatient clinics also used radiological assessment as part of their inclusion criteria. All participants received oral antibiotics and were assigned to either oral corticosteroids (prednisone 24-80 mg daily or betamethasone 1 mg daily) or control treatment (placebo in three trials and non-steroidal anti-inflammatory drugs in one trial). In all trials, participants treated with oral corticosteroids were more likely to have short-term resolution or improvement of symptoms than those receiving control treatment: at Days 3 to 7, risk ratio (RR) 1.4, 95% CI 1.1-1.8; risk difference (RD) 20% (6% to 34%) and at Days 4 to 10 or 12, RR 1.3, 95% CI (1.0-1.7), RD 18% (3% to 33%). An analysis of the three trials with placebo as control treatment revealed similar results but with lesser effect size: Days 3 to 6: RR 1.2, 95% CI (1.1-1.4), RD 12% (5% to 19%) and Days 4 to 10 or 12: RR 1.1, 95% CI (1.0-1.2), RD 10% (3% to 16%). Scenario analysis demonstrated that outcomes missing from the trial reports may have introduced attrition bias. We did not identify any data on long-term effects of oral corticosteroids on this condition, such as effects on relapse or recurrence rates. Reported side-effects of oral corticosteroids were limited and mild.

Conclusion

Current evidence suggests that oral corticosteroids as an adjunctive therapy to oral antibiotics are effective in short-term relief of symptoms in ARS. However, data are limited and there is a significant risk of bias. High quality trials assessing the efficacy of systemic corticosteroids both as an adjuvant and a monotherapy in patients with ARS in general practice should be initiated.

Introduction

Acute rhinosinusitis (ARS) is an important reason for consultations in general practice, with typically 50 cases seen by a general practitioner annually.[1 2] This condition is associated with symptoms such as facial pain, headache and nasal congestion which can be unpleasant for many people.[3] As a consequence, patients may seek medical attention in order to relieve symptoms and shorten the illness duration. Patients' misconceptions on the effectiveness of antibiotics in viral infections[4] and physicians' overestimation of patients' expectations towards antibiotic prescriptions[5 6] along with the lack of specific knowledge about respiratory tract infections[7], are probably the main reasons for high antibiotic prescription rates in daily practice.[1 2] However, a recent systematic review and a meta-analysis of individual data of randomised controlled trials (RCTs) revealed that antibiotics are of limited use in patients with ARS.[8 9] ARS is therefore associated with both high direct and indirect health care costs and contributes to antimicrobial resistance.

Description of the condition

ARS is defined as inflammation and swelling of the (para)nasal mucous membranes.[10 11] It is thought that this mucosal swelling leads to obstruction of sinus openings, impairment of mucous drainage, sinus ventilation and mucociliary clearance leading to the characteristic signs and symptoms of ARS such as purulent nasal discharge, nasal obstruction, reduction or loss of smell, headache, facial pain/pressure and/or dental pain.[10] In general practice, diagnosing ARS is usually based on signs and symptoms, since the diagnostic value of laboratory measurements (such as C-reactive protein, erythrocyte sedimentation rate and white blood cell count) is low[12 13] and imaging (such as sinus X-ray and sinus ultrasound) leads to a high number of false positive and negative results.[14 15] The use of more advanced and invasive diagnostic tools such as nasal endoscopy, computed tomography (CT) scanning and sinus puncture are limited to secondary or tertiary care settings.

There is considerable debate about the aetiology of clinically diagnosed ARS. The condition was thought to be due to a bacterial infection of the paranasal sinuses.[16] However, the majority of cases of ARS are likely to be caused by viral pathogens, since only 0.5% to 2% of viral upper respiratory tract infections are complicated by bacterial infection.[17 18] Moreover, the results of a systematic review of RCTs with antibiotics have demonstrated only modest beneficial effect sizes[8] and a recent meta-analysis of individual patient data confirms that antibiotics are of limited use in clinically diagnosed ARS, even when patients do report signs and symptoms for 10 days.[9]

As a consequence, acute inflammation of the (para)nasal mucosa due to (viral) pathogens might be the predominant common path in the causation of clinically

diagnosed ARS.[11] [19] Additionally, some studies suggest that non-infectious processes such as allergic inflammation and local eosinophila may also play an important role.[20] [21] Therefore, it is possible that anti-inflammatory therapy could provide attenuation of the host inflammatory response, leading to reductions in mucosal oedema and enhanced sinus clearance.

Description of the intervention

Corticosteroids inhibit transcription of pro-inflammatory mediators in human airway endothelial cells[22] and could potentially act as anti-inflammatory and decongestant agents. As a consequence, the use of corticosteroids might have beneficial effects in patients with ARS. A recent systematic review assessed the role of intranasal but not systemic corticosteroids for ARS.[23] It found that for every 100 patients treated with intranasal corticosteroids (INCS), seven additional patients had complete or marked symptom relief at 15 to 21 days (NNT = 15). In a subsequent RCT, INCS did not provide an overall beneficial effect.[24] However, INCS therapy tended to be more effective in mild than severe cases, leading to the suggestion that thick secretions and severe inflammation in the nasal passages limited the effective topical delivery of the corticosteroids.

How the intervention might work

Systemic administration of corticosteroids might allow more effective delivery of corticosteroids to the nasal and (para)nasal mucosa than topical steroids, providing increased anti-inflammatory effects. This could lead to a reduction in nasal oedema, mucus production and sinus blockage, which could result in symptomatic relief. Systemic corticosteroids (alone or as adjunctive treatment) are effective at reducing the severity of some acute respiratory tract infections such as croup[25] and sore throat[26], as well as inflammatory conditions such as asthma and exacerbations of chronic obstructive airways disease.[27] When implementing systemic corticosteroid therapy in practice, physicians should be aware of the absence of specific contraindications including (active) peptic ulcer disease, history of depression or psychosis and immunodeficiency. Immunocompromised patients have an increased risk for bacterial (super)infection during viral (respiratory tract) infections and the use of systemic corticosteroids might further enhance this probability.

Why it is important to do this review

There has not been a systematic review of systemic corticosteroids for ARS. The beneficial effects of INCS are modest but it is unclear if this is due to poor delivery of corticosteroids due to blocked nasal passages, or lack of anti-inflammatory effect in ARS. This systematic review examines the effects of systemic corticosteroids in patients with ARS in order to provide a more definite answer on the use of corticosteroids for this condition.

Objectives
1. To assess the effectiveness of systemic corticosteroids on clinical response rates in children and adults with ARS.
2. To determine adverse effects and relapse rates of treatment with systemic corticosteroids compared to placebo or standard clinical care for ARS in children and adults.

Methods

Types of studies
RCTs comparing systemic corticosteroids to placebo or standard clinical care.

Types of participants
Children and adults with ARS. ARS was defined by clinical diagnosis alone, or confirmed by additional radiological and/or nasal endoscopic examination. We excluded studies examining participants with a diagnosis of chronic sinusitis (defined as more than 12 weeks' duration) or other clear diagnoses (e.g. common cold or nasal polyposis).

Types of interventions
Studies which used systemic corticosteroids versus placebo or standard clinical care in the control group. We included trials of corticosteroids delivered orally, or parenterally by intravenous or intramuscular injection. We excluded trials of cortico-steroids delivered by intranasal route or by inhalation. We included trials reporting combined interventions (e.g. co-treatment with antibiotics) if they allowed a direct comparison between the systemic corticosteroid and the control group and were unconfounded. By unconfounded, we mean studies where the two groups were not treated differently, except for the delivery of systemic corticosteroids to one group.

Primary outcome
1. Proportion of participants with resolution or improvement of any patient-related symptoms, including total change in clinical status, measured at two time points - short-term (≤ two weeks) or long-term (> two weeks).

Secondary outcomes
1. Time lapse before resolution of symptoms;
2. Relapse rate;
3. Adverse events.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 2, which includes the Acute Respiratory Infections (ARI) Group's Specialised Register, the Database of Reviews of Effects (DARE) (2011, Issue 2) and the NHS Health Economics Database (2011, issue 2), part of The Cochrane Library, www.thecochranelibrary.com (accessed 17 June 2011; MEDLINE (1966 to June week 2, 2011) and EMBASE (January 2009 to June week 2, 2011). The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) Ovid format. See Appendix 1 for the search strategies.

To increase the yield of relevant studies, the reference lists of all identified studies and reviews were inspected. There were no language or publication restrictions.

Data collection

Two review authors (RV, MT) independently screened titles and abstracts of the electronic searches and reviewed the full text of the potentially relevant titles and abstracts against the inclusion and exclusion criteria.

Data extraction

Two review authors (RV, MT) extracted data from the included trials and disagreements were resolved by discussion. We extracted the following information from each trial:

1. characteristics of trials: setting, design, method of data-analysis;
2. participants: study population, number of participants in each group, patient characteristics such as age and gender;
3. type of intervention used: dosage, route of administration, duration of treatment and follow up, compliance, co-interventions;
4. outcomes: resolution or improvement of any patient-related symptoms, adverse events related to the intervention, drop-outs and reason(s) for dropping out.

Assessment of risk of bias in included studies

Two review authors (RV, MT) independently assessed the methodological quality. We resolved any disagreements by discussion. We assessed the methodological quality of the included studies based on random sequence generation, allocation concealment, blinding, completeness of data and outcome assessment. Results of the risk of bias assessment were presented in 'Risk of bias tables' and a 'Risk of bias summary' figure.

Measures of treatment effect

We performed intention-to-treat (ITT) analyses. We categorised the primary outcome (proportion of participants with resolution or improvement of individual clinical features) into short-term (≤ two weeks) or long-term (> two weeks). We expressed dichotomous outcomes as risk ratios (RR) and risk difference (RD) with 95% confidence intervals (CIs).

Dealing with missing data

We tried to contact the trial authors to provide additional information in case of missing data. In primary analyses, we only analysed the available data based on the ITT principle. We explored the impact of the incomplete data reporting on the validity of our results by performing scenario analyses (best and worst case scenario). In the best-case scenario analyses all participants who were lost to follow-up in the treatment group were counted as treatment successes and all participants lost to follow up in the control group were counted as treatment failures. In contrast, in the worst-case scenario analyses all participants who were lost to follow-up in the treatment group were counted as treatment failures and all participants lost to follow up in the control group were counted as treatment successes.

Assessment of heterogeneity

We assessed clinical heterogeneity of the trials. We used the I^2 statistic[28] to measure the level of statistical heterogeneity for each outcome. We used a fixed-effect meta-analysis where no heterogeneity was present. We looked for the direction of effect and where applicable and used a random-effects model where substantial heterogeneity (I^2 above 50%) was detected.

Assessment of reporting bias

We assessed reporting bias using a funnel plot.

Subgroup analysis and investigation of heterogeneity

If sufficient data were available, we considered subgroup analyses for:

1. adult/child;
2. type and route of delivery of corticosteroid;
3. duration and dose of corticosteroid;
4. radiological improvement versus clinical improvement;
5. radiological versus clinical diagnosis.

Sensitivity analysis

We performed sensitivity analysis by removing single trials to investigate the extent to which they contributed to the heterogeneity, particularly looking at reasons for clinical heterogeneity of the studies (e.g. type of control treatment).

Results

Description of studies

For details on study design, participants, interventions and outcomes of each included trial see: Characteristics of included studies (Appendix 2). Main reasons for excluding studies from the review are shown in: Characteristics of excluded studies (Appendix 3).

Results of the search

We retrieved a total of 2630 records from the initial search of CENTRAL, MEDLINE and EMBASE. Removing duplicates left 1710. After screening titles and abstracts we identified seven potentially eligible studies. We obtained their full text papers and excluded three trials as they studied chronic sinusitis.[29-31] This left four trials eligible for inclusion.[32-35] We identified no additional eligible trials after scanning the reference lists of full text papers.

Included studies

Four trials with a total of 1008 participants involved adults only. One trial was a 2 x 2 factorial design[33] and the other three were parallel designs.[32 34 35] In all four trials ARS was defined clinically. However, three trials[32-34] also included radiological assessment as part of their inclusion criteria. These three studies, performed in France, included participants recruited from ear, nose and throat (ENT) outpatient clinics.[32-34] One trial, performed in South Africa, included participants recruited from general practices.[35]

Interventions in the trials included oral (methyl)prednisone (24 mg to 80 mg) for three, five and seven days and oral betamethasone 1 mg for five days. The control group received a placebo in three studies[33-35] and a non-steroidal anti-inflammatory drug (NSAID) in one study.[32] All participants in all four studies also received oral antibiotics: amoxicillin-clavulanic acid[33 35], cefpodoxime[34] or pristinamycin.[32]

The use of analgesics (i.e. paracetamol) was included as an outcome measure in two studies.[34 35] No symptomatic relief medication was permitted in one study[32], while the other study did not report any information on the use of additional medications.[33]

The included studies reported the proportion of participants with therapeutic success on Day 7 [32], proportions of participants experiencing pain relief on Day 4 [33], global response to treatment on Day 3 and Day 10 to 12 [34], improvement of symptoms from Day 0 to Day

6 and the percentage of participants with physical signs present or absent on Day 0 and Day 6.[35] All studies reported on the number of adverse events. In two studies the adverse events were reported both by patients (questionnaire) and investigator (at site visits)[32 34] while the adverse events in the other studies were reported by the investigator[33] or the patients[35] only. For more details on the outcome measures of the included studies see: Characteristics of included studies (Appendix 2).

Excluded studies

We excluded three trials after reviewing the full text, as they studied the effectiveness of systemic corticosteroids in participants with chronic sinusitis (Appendix 3).[29-31] For details on ongoing studies see: Characteristics of ongoing studies (Appendix 4).

Risk of bias in included studies

We judged the methodological quality of the included trials to be moderate (Figure 1). For details on the risk of bias in included studies see: 'Risk of bias tables' (Table 1).

Figure 1. Risk of bias summary

Table 1. Risk of bias tables

Cannoni 1990		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	Unclear risk	Blinding procedure not described
Incomplete outcome data (attrition bias)	Unclear risk	Complete case analysis performed
Other bias	Unclear risk	ITT analysis - unclear Baseline characteristics - not described

Gehanno 2000		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	Unclear risk	Blinding procedure not described
Incomplete outcome data (attrition bias)	Unclear risk	Complete case analysis performed
Other bias	Unclear risk	ITT analysis - yes Baseline characteristics - not described

Klossek 2004		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias)	Unclear risk	Blinding procedure not mentioned
Incomplete outcome data (attrition bias)	Unclear risk	Reasons for drop-outs not reported, complete case analysis performed
Other bias	Low risk	ITT analysis – yes Baseline characteristics – balanced

Ratau 2004		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computed-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias)	Unclear risk	Blinding procedure not mentioned
Incomplete outcome data (attrition bias)	Unclear risk	Not described
Other bias	Unclear risk	ITT analysis – unclear Baseline characteristics - not described, outcome - no absolute numbers provided

Allocation (selection bias)

All four studies stated they used randomisation, but none of the studies reported concealment of allocation and the methods of randomisation were unclear in three of the four trials.[32-34] Additionally, only one trial did report baseline characteristics of participants.[34]

Blinding (performance bias and detection bias)

We considered all four trials to be double-blinded but there were insufficient details to determine if this referred to participants, outcome assessors or study personnel.

Incomplete outcome data (attrition bias)

Three trials reported the numbers of participants who failed to complete the trial[32-34], whereas in one trial[35] this was not reported and it was assumed that there were no drop-outs. The total loss to follow-up was 8%[34], 4%[33] and 7%[32], respectively. In two of these studies[33 34] the number of participants who were lost to follow up was higher in the treatment group, whereas in the other study[32] the drop-out rate was higher in the control group (NSAID).

Selective reporting (reporting bias)

Two studies used ITT analyses[33 34], while in the other two this was not clear.[32 35] Additionally, one trial did not provide information on absolute numbers of patients with resolution of symptoms as only percentages were reported.[35]

Other potential sources of bias

No other potential sources of bias could be detected in the four included trials.

Effects of interventions

For numerical details see: Tables 2-5. We identified four studies that included a total number of 1008 participants that met our inclusion criteria.[32-35] From these trials, data from a total of 945 participants could be extracted for meta-analyses for the primary outcome.

Primary outcome

Information on the primary outcome could be retrieved from all four trials but at different time points. One trial reported global response to treatment on both Day 3 and Days 10 to 12 [34], whereas three trials reported the outcome of interest at one point in time: the proportions of participants experiencing pain relief on Day 4 [33], proportions

of participants with physical signs present or absent at Day 6 [35] and therapeutic success at Day 7.[32] When combining data from the four trials, we calculated two effect estimates for the primary outcome, ranging from Days 3 to 7 and Days 4 to 10 or 12.[32-35] Participants treated with oral corticosteroids were more likely to have short-term resolution or improvement of symptoms than those receiving the control treatment (placebo or NSAIDs) at Days 3 to 7, RR 1.4, 95% CI (1.1 to 1.8), RD 20% (6% to 34%) (Figure 2) and at Days 4 to 10/12, RR 1.3, 95% CI (1.0 to 1.7), RD 18% (3% to 33%) (Figure 3). However, statistical heterogeneity was high in both of these analyses (I^2 statistic ≥ 75%).

Table 2. Results: primary analysis - oral corticosteroids versus placebo or NSAID

Outcome or Subgroup	Studies	N	Measure of association	Effect estimate
2.1 Proportion of patients with resolution or improved symptoms at days 3 to 7	4	869	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.08, 1.81]
2.1.1 very short-term (days 3 to 4) 2		624	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.05, 1.32]
2.1.2 short-term (days 6 to 7)	2	245	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.44, 2.31]
2.2 Proportion of patients with resolution or improved symptoms at days 4 to 10 or 12	4	945	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.04, 1.68]

Figure 2. Forrest plot primary analysis - oral corticosteroids vs. placebo or NSAID - Days 3 to 7
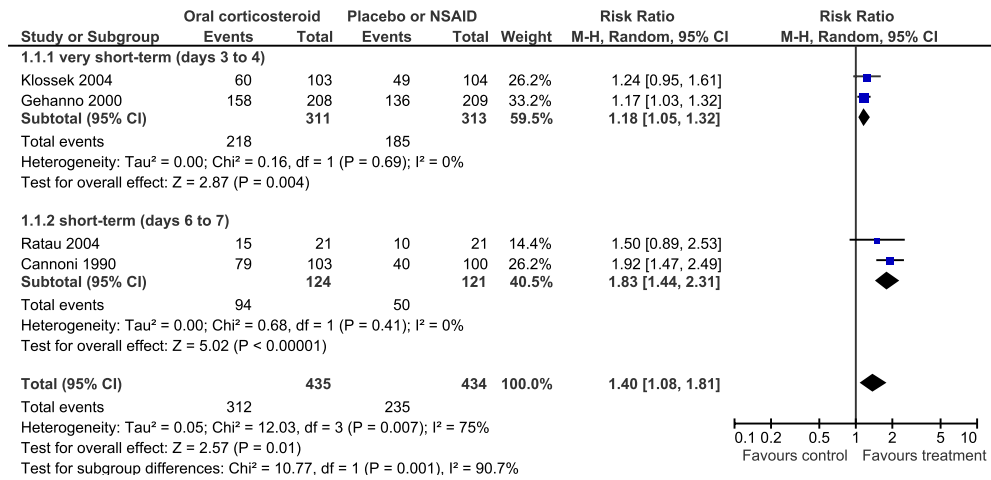
Figure 3. Forrest plot primary analysis - oral corticosteroids vs. placebo or NSAID - Days 4 to 10/12
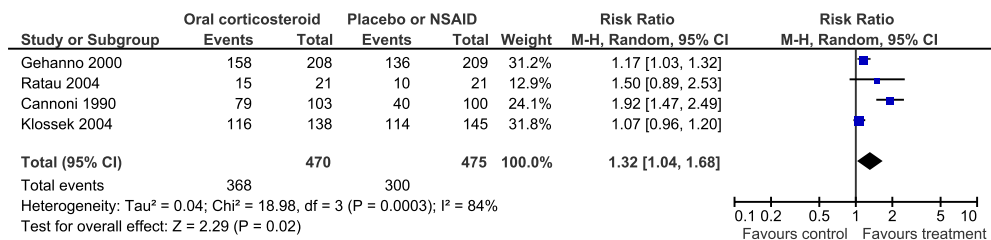
We therefore performed a sensitivity analysis by removing the trial with NSAIDs as a control treatment.[32] Sensitivity analyses on the three trials with a placebo as the control treatment[33-35] demonstrated similar direction of the effect but to a lesser extent, Days 3 to 6, RR 1.2, 95% CI (1.1 to 1.4), RD 12% (5% to 19%) (Figure 4) and Days 4 to 10/12, RR 1.1, 95% CI (1.0 to 1.2), RD 10% (3% to 16%) (Figure 5). Statistical heterogeneity was low in these sensitivity analyses (I^2 statistic $\leq$ 17%).

Table 3. Results: sensitivity analysis - oral corticosteroids versus placebo

Outcome or Subgroup	Studies	N	Measure of association	Effect estimate
3.1 Proportion of patients with resolution or improved symptoms at days 3 to 6	3	666	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.07, 1.35]
3.2 Proportion of patients with resolution or improved symptoms at days 4 to 10 or 12	3	742	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.04, 1.24]

Figure 4. Forrest plot sensitivity analysis - oral corticosteroids vs. placebo - Days 3 to 6
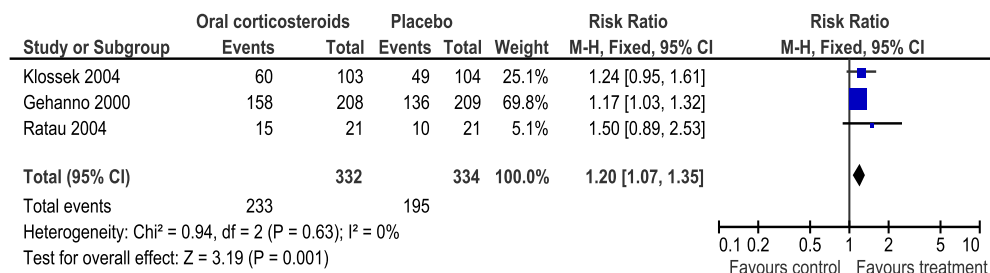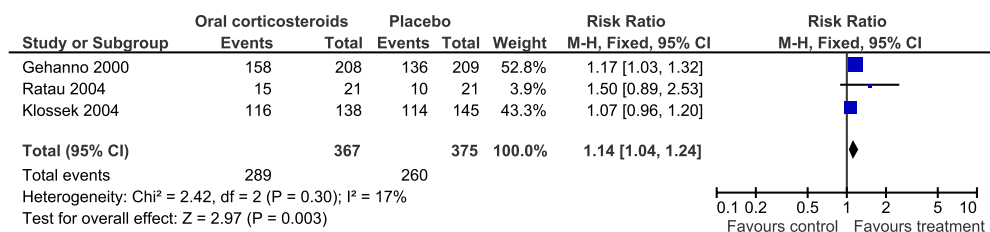

Figure 5. Forrest plot sensitivity analysis - oral corticosteroids vs. placebo - Days 4 to 10/12

In scenario analyses the best case did reveal increased beneficial effect sizes for short-term relief of oral corticosteroids (Table 4.1, Table 4.3, Table 5.1, Table 5.3), whereas worst-case scenario revealed no statistically significant beneficial effect of oral corticosteroids (Table 4.2, Table 4.4, Table 5.2, Table 5.4). No data on long-term effects (> two weeks) of oral corticosteroids could be extracted from the trials.

Table 4. Results: scenario analysis - oral corticosteroids versus placebo or NSAID

Outcome or Subgroup	Studies	N	Measure of association	Effect estimate
4.1 Proportion of patients with resolution or improved symptoms at days 3 to 7 Best case scenario	4	1008	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.15, 2.64]
4.2 Proportion of patients with resolution or improved symptoms at days 3 to 7 Worst case scenario	4	1008	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.72, 1.66]
4.3 Proportion of patients with resolution or improved symptoms at days 4 to 10 or 12 Best Case scenario	4	1008	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.12, 1.82]
4.4 Proportion of patients with resolution or improved symptoms at days 4 to 10 or 12 Worst Case scenario	4	1008	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.93, 1.52]

Table 5. Results: scenario analysis - oral corticosteroids versus placebo

Outcome or Subgroup	Studies	N	Measure of association	Effect estimate
5.1 Proportion of patients with resolution or improved symptoms at days 3 to 6 Best case scenario	3	789	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.97, 2.69]
5.2 Proportion of patients with resolution or improved symptoms at days 3 to 6 Worst case scenario	3	789	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.57, 1.59]
5.3 Proportion of patients with resolution or improved symptoms at days 4 to 10 or 12 Best case scenario	3	789	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.11, 1.32]
5.4 Proportion of patients with resolution or improved symptoms at days 4 to 10 to 12 Worst case scenario	3	789	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.26]

Secondary outcomes

Time lapsed before resolution of symptoms
No data on this outcome were reported in the trials.

Adverse events
No serious adverse events were reported in the studies. There was no significant difference in the occurrence of mild adverse events (i.e. abdominal pain, diarrhoea) and discontinuation of study treatment due to adverse events between the corticosteroid group and the placebo groups.[33-35] In one trial 7 adverse events were rated as severe by the patient: 3 in corticosteroid group (1 diarrhoea, 1 acute gastroenteritis, 1 abdominal pain) versus 4 in placebo group (1 vomiting, 1 abdominal pain, 1 neuralgia, 1 ear pain).[35] In the trial that used a NSAID as control group[32], the number of adverse events was significantly higher in the NSAID group (51 adverse events in 35 participants) as compared to the corticosteroid group (23 adverse events in 18 participants). In addition, discontinuation of study participation due to adverse events occurred in seven participants from the NSAID group versus none in the prednisolone group.

Bacteriological cure and relapse rates
No data on these outcomes could be extracted from the trials.

Subgroup analysis
Treatment effect of oral corticosteroid was larger at the short-term time point (Days 6-7) than at very short-term time point (Days 3-4) (Figure 2). Other subgroup analyses were not performed as the included trials did not report data for these prespecified subgroups.

Discussion

Four trials with a total of 1008 adult participants were included in this review. When combining results of these studies, ARS patients treated with oral corticosteroids were more likely to have short-term improvement or resolution of symptoms than those receiving control treatment (placebo or NSAIDs), at Days 3 to 7 (RD 20%) and Days 4 to 10 or 12 (RD 18%). Moreover, side-effects of oral corticosteroids reported in these studies were limited and mild.

Overall completeness and applicability of evidence
Before applying these results to practice, there are important limitations which may have

had an impact on our results. Only four studies with a limited number of participants met the inclusion criteria for this review. Additionally, these studies only provided data on the effectiveness of oral corticosteroids up to Day 10 to 12. Therefore, their long-term (> two weeks) effects are unclear. Moreover, the effect of systemic corticosteroids on relapse rates of ARS is unknown. Besides, all participants in the four included studies also received oral antibiotics. Although the contribution of antibiotics to resolution of ARS might be modest, we were unable to determine the independent effect of systemic corticosteroids. Finally, the majority of the included patients in this review has been recruited in ENT outpatient clinics as only one small trial (with 42 participants)[35] has been performed in general practice. This is in contrast to daily practice in which most of the patients with ARS are seen in general practice.

Quality of the evidence

We judged the included studies to have a moderate methodological quality, which may have led to biased estimates of effect. All four studies stated that they were randomised and double-blinded but none adequately reported the blinding procedure, while only one trial contained an adequate report of the generation of allocation sequence. Moreover, three of the four studies performed complete case-analysis (excluding participants who were lost to follow up from their analysis) which might have important implications for the validity of their results since missing values are rarely completely at random. To investigate the potential impact of the incomplete data reporting on our results, we performed scenario analysis (best and worse-case scenarios). Scenario analyses revealed that outcomes missing in the trials might have introduced attrition bias since worst-case scenario revealed no statistically significant beneficial effect of oral corticosteroids.

Potential biases in the review process

There was some clinical heterogeneity among the included trials. ARS was defined clinically in all trials but the three trials performed in ENT outpatient clinics also included radiological assessment as part of their inclusion criteria. Besides, duration and dosage of the intervention (prednisolone for three, five and seven days (24 mg to 80 mg) and betamethasone 1 mg for five days), type of control treatment (one trial used NSAIDs as a control treatment) and the follow up time did vary across the studies. Additionally, all four trials used different outcome assessments, varying from pain relief to global response to treatment. Combining multiple endpoints might lead to invalid results (type 1 error). However, the results of the four separate studies are practically equal. Nevertheless, one could argue that (statistical) heterogeneity in primary analyses was too high to present pooled results (I^2 statistic $\geq 75\%$). However, the consistency of the I^2 statistic is known to

be limited when only few studies are available and subjective assessment could be made. To enhance the validity of our results, we performed additional analyses on the three trials with the placebo as the control treatment. These analyses demonstrated similar results as primary analyses but with low (statistical) heterogeneity (I^2 statistic ≤ 17%). In addition, we assessed funnel plots for potential reporting biases for primary analysis. No asymmetry could be detected based on the four included trials (Figure 6).

Figure 6. Funnel plot
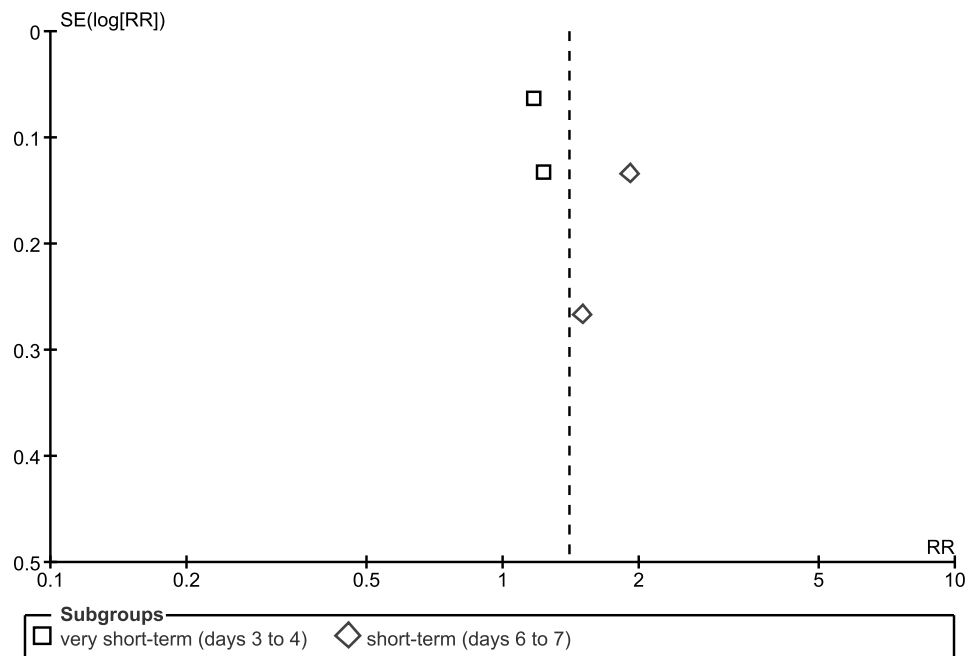
Agreements and disagreements with other studies or reviews

No previous review on the use of systemic corticosteroids in ARS has been performed. A recent systematic review on INCS (with or without antibiotics) for ARS reported only a modest beneficial effect size (NNT = 15).[23] Since we could only evaluate the effects on systemic corticosteroids in short-term relief (≤ 2 weeks), a valid comparison between these reviews cannot be made. However, in a subsequent RCT performed in general practice, INCS as a monotherapy did not provide an overall beneficial effect in short-term symptom relief.[24] Since the data in our review has a significant risk of bias, additional trials should be initiated to determine the true benefits of systemic corticosteroids in both short-term and long-term symptom relief in patients with ARS in general practice.

Conclusions

Implications for practice
Current evidence suggests that oral corticosteroids as adjunctive therapy to oral antibiotics are effective in short-term relief of symptoms in ARS. However, data are limited and there is a significant risk of bias.

Implications for research
Since evidence on the use of corticosteroids in patients with ARS is scarce, high quality trials assessing the efficacy of systemic corticosteroids both as an adjuvant and a monotherapy in general practice should be initiated to provide a more definite answer on their benefits.

Appendix 1. Search strategy

Database	Search strategy
MEDLINE and CENTRAL	1 exp Sinusitis/ 2 sinusit*.tw. 3 (rhinosinusit* or nasosinusit*).tw. 4 ((sinus* or paranasal or para-nasal or nasopharynx or naso-pharynx) adj3 (infect* or inflam*)).tw. 5 purulent nasal discharge*.tw. 6 (nasal adj3 obstruct*).tw. 7 Rhinitis/ 8 rhinit*.tw. 9 or/1-8 10 Adrenal Cortex Hormones/ 11 corticosteroid*.tw,nm. 12 exp Glucocorticoids/ 13 exp Hydroxycorticosteroids/ 14 exp Pregnenediones/ 15 hydrocortisone.tw,nm. 16 hydroxypregnenolone.tw,nm. 17 pregnenolone.tw,nm. 18 tetrahydrocortisol.tw,nm. 19 cortodoxone.tw,nm. 20 cortisone.tw,nm. 21 corticosterone.tw,nm. 22 hydroxycorticosteroid*.tw,nm. 23 glucocorticoid*.tw,nm. 24 triamcinolone.tw,nm. 25 prednisone.tw,nm. 26 prednisolone.tw,nm. 27 paramethasone.tw,nm. 28 methylprednisolone.tw,nm. 29 dexamethasone.tw,nm. 30 clobetasol.tw,nm. 31 beclomethasone.tw,nm. 32 betamethasone.tw,nm. 33 budesonide.tw,nm. 34 steroid*.tw,nm. 35 (efcortesol or hydrocortone or solu- cortef).tw,nm. 36 (betnelan or betnesol).tw,nm. 37 (deflazacort or calcort).tw,nm. 38 (medrone or solu-medrone or depo-medrone).tw,nm. 39 kenalog.tw,nm. 40 (novolizer or pulmicort or symbicort).tw,nm. 41 (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw. 42 or/10-41 43 9 and 42
Embase.com	1. 'sinusitis'/exp 2. sinusit*:ab,ti 3. 'rhinosinusit'/de 4. rhinosinusit*:ab,ti OR nasosinusit*:ab,ti 5. ((sinus* OR paranasal OR 'para nasal' OR nasopharynx OR 'naso pharynx') NEAR/3 (infect* OR inflam*)):ab,ti 6. 'purulent nasal discharge':ab,ti 7. (nasal NEAR/3 obstruct*):ab,ti 8. 'rhinitis'/de 9. rhinit*:ab,ti 10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 11. 'corticosteroid'/de 12. corticosteroid*:ab,ti 13. 'glucocorticoid'/exp OR 'hydroxycorticosteroid'/de OR 'pregnane derivative'/de 14. pregnenedione*:ab,ti 15. hydrocortisone:ab,ti 16. hydroxypregnenolone:ab,ti 17. pregnenolone:ab,ti 18. tetrahydrocortisol:ab,ti 19. cortodoxone:ab,ti 20. cortisone:ab,ti 21. corticosterone:ab,ti 22. hydroxycorticosteroid*:ab,ti 23. glucocorticoid*:ab,ti 24. triamcinolone:ab,ti 25. prednisone:ab,ti 26. prednisolone:ab,ti 27. paramethasone:ab,ti 28. methylprednisolone:ab,ti 29. dexamethasone:ab,ti 30. clobetasol:ab,ti 31. beclomethasone:ab,ti OR beclometasone:ab,ti 32. betamethasone:ab,ti 33. budesonide:ab,ti 34. steroid:ab,ti 35. efcortesol:ab,ti OR hydrocortone:ab,ti OR 'solu cortef':ab,ti 36. betnelan:ab,ti OR betnesol:ab,ti 37. deflazacort:ab,ti OR calcort:ab,ti 38. medrone:ab,ti OR 'solu medrone':ab,ti OR 'depo medrone':ab,ti 39. kenalog:ab,ti AND [embase]/lim 40. novolizer:ab,ti OR pulmicort:ab,ti OR symbicort:ab,ti 41. aerobec:ab,ti OR asmabec:ab,ti OR beclazone:ab,ti OR becodisks:ab,ti OR becotide:ab,ti OR qvar:ab,ti OR becloforte:ab,ti OR 'clenil modulite':ab,ti 42. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 43. #10 AND #42 44. 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp 45. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR allocat*:ab,ti OR assign*:ab,ti OR ((singl* OR doubl*) NEAR/2 (mask* OR blind*)):ab,ti 46. #44 OR #45 47. #43 AND #46

Appendix 2. Characteristics of included studies

Cannoni 1990	
Methods	**Randomised -** yes, method of randomisation not described
	Concealment of allocation - not described
	Double-blind - yes, blinding procedure not described
	Intention-to-treat (ITT) - unclear
	Loss to follow up - described; 203 patients (93%) completed study
	Design - parallel
Participants	**N =** 219
	Age = 15 to 70 years
	Inclusion criteria: acute, non-allergic sinusitis confirmed by radiology and nasal endoscopy
	Exclusion criteria: allergic sinusitis (allergic rhinitis, nasal polyposis), previous sinonasal surgery, contraindication for study treatment and treatment with corticosteroids, antibiotics or NSAIDs 15 days preceding recruitment
	Baseline characteristics - not described
	Participants recorded symptoms twice a day and were examined at day 0 and day 7
Interventions	All participants in both groups received pristinamycin (antibiotic) 1000 mg twice daily
	Tx - prednisolone 40 mg once daily for participants with a weight < 60 kg and prednisolone 60 mg once daily for participants with a weight > 60 kg, for 7 days; N = 107 (N = 103 in analysis)
	C group - niflumic acid (NSAID) 250 mg 3 daily for 7 days; N = 112 (N = 100 in analysis)
	Use of additional medication - other anti-inflammatory drugs, intranasal medication and analgesics were not permitted
Outcomes	**Primary outcome:** Therapeutic success, defined as a combination of resolution of spontaneous pain, absence of sinus pain on palpation, absence of nasal discharge or nasal discharge without purulence and a clean appearance of the middle meatus at nasal endoscopy at Day 7
	Secondary outcome: Adverse events
Notes	**Setting -** secondary care setting in France, 50 otorhinolaryngologists participated in the trial
	Drop-outs total - 16/219 (7%)
	Drop-outs from Tx - 4 (3.7%) - 4 loss to follow up
	Drop-outs from C group - 12 (12.7%): 2 loss to follow up, 7 adverse events, 3 ineffectiveness

Gehanno 2000	
Methods	**Randomised -** yes, method of randomisation not described
	Concealment of allocation - not described
	Double-blind - yes, blinding procedure not described
	Intention-to-treat (ITT) - yes
	Loss to follow up - described; 417 patients (96%) completed study
	Design – 2 x 2 factorial design
Participants	**N =** 433
	Age = 18 years or older
	Inclusion criteria: less than 10 days of acute sinusitis defined by craniofacial pain, purulent nasal discharge with purulent drainage from the middle meatus, and opacities with or without air-fluid levels on standard X-ray or CT scan
	Exclusion criteria: acute sinusitis requiring immediate surgical drainage, acute exacerbations of chronic sinusitis, contraindication for study treatment and treatment with antibiotics or corticosteroids 15 days preceding recruitment
	Baseline characteristics - not described
	Participants were contacted by telephone on Day 4 +/-1 to evaluate craniofacial pain, nasal discharge and temperature. Clinical and radiological follow-up was performed on Day 14 +/- 2, incl. assessment of safety.
Interventions	From days 0-5, all participants received amoxicillin-clavulanic acid (ACA) 500 mg three daily
	From days 0-5, participants were randomised to either:
	Tx - methylprednisolone 8 mg three daily (Tx); N = 219 (N = 208 included in ITT analysis); or
	C group – placebo; N = 214 (N = 209 included in ITT analysis)
	From days 6-10, participants received either ACA 500 mg three daily or placebo
	Use of additional medication - not described
Outcomes	**Primary outcome:** Therapeutic success, defined as clinical recovery on Day 14, with or without radiological normalisation. The other cases were considered failures.
	Secondary outcome: i) course of symptoms on Day 4
	ii) symptoms and possible radiological signs on Day 30
	The effectiveness of short-course corticosteroid was of secondary interest in this study; only data on Day 4 of treatment were provided for corticosteroid therapy
Notes	**Setting -** secondary care setting in France, 51 private otorhinolaryngologists.
	Drop-outs total - 16/433 (4%) - lack of data 13; protocol violation 3
	Drop-outs from Tx - 11 (5.0%)
	Drop-outs from C group - 5 (2.3%)

Klossek 2004	
Methods	**Randomised -** yes, method of randomisation not described **Concealment of allocation -** not described **Double-blind -** yes, blinding procedure not described **Intention-to-treat (ITT) -** yes **Loss to follow up -** yes, reasons not described; 289 participants (92%) completed study **Design -** parallel
Participants	**N =** 314 **Age =** 18 years or older **Inclusion criteria:** acute sinusitis, confirmed by X-ray and nasal endoscopy, for less than 5 days, with spontaneous pain assessed as > 50 mm on a visual analogue scale (VAS) **Exclusion criteria:** acute sinusitis requiring immediate surgical drainage, allergic rhinitis, nasal polyposis, contraindication for study treatment, treatment with antibiotics in previous 3 months or (intranasal or systemic) corticosteroids 3 days preceding recruitment **Baseline characteristics -** balanced Patients underwent X-ray and nasal endoscopic examination at Day 1, 10-12 and 28- 32. Participants recorded symptoms from Day 1-3 and were contacted by telephone on Day 4
Interventions	All participants received cefpodoxime (antibiotic) 200 mg twice daily from days 1-10 **Tx -** prednisone 0.8 to 1.2 mg/kg (weight 40 to 60 kg: 40 mg, weight 60 to 80 kg: 60 mg, weight > 80 kg: 80 mg) for 3 days; N = 157 (N = 142 included in ITT analysis) **C group –** placebo for 3 days; N = 157 (N = 147 included in ITT analysis) **Use of additional medication -** paracetamol 1000 mg 8-hourly for pain as needed, other symptomatic relief medication not described
Outcomes	**Primary outcome:** Mean of the differences between pain at baseline and Day 3 measured using the VAS (this was termed the mean pain intensity difference - MPID) **Secondary outcomes:** i) mean of the differences in intensity of nasal obstruction ii) time lapse before the orally expressed relief of pain (pain relief intensity difference - PRID) iii) administration of paracetamol during the first 3 days iv) global effect of treatment scored by patient at Day 3 v) global effect of treatment scored by participant at Day 10-12
Notes	**Setting -** secondary care setting in France, 80 otorhinolaryngologists within 8 regions **Drop-outs total -** 25/314 (8%) - reasons unknown **Drop-outs from Tx -** 15 (9.5%) **Drop-outs from C group -** 10 (6.4%)

Ratau 2004	
Methods	**Randomised -** yes, computer-generated random numbers
	Concealment of allocation - not described
	Double-blind - yes, blinding procedure not described
	Intention-to-treat (ITT) - unclear
	Loss to follow up - not described
	Design - parallel
Participants	**N =** 42
	Age = 29 years (mean age)
	Inclusion criteria: clinically defined acute sinusitis for less than 12 weeks. Total symptom score (7 symptoms, scored 0-3 severity, to maximum score of 21) was ≥ 6, at least one nasal symptom had to be moderate or severe and purulent rhinorrhoea or postnasal drip had to be present
	Exclusion criteria: nasal polyposis, abnormalities of the nose, contraindication for study treatment, treatment with antibiotics, anti-inflammatory agents, oral corticosteroids in previous 4 weeks or intranasal corticosteroids 2 weeks preceding recruitment
	Baseline characteristics - not described
	Participants evaluated symptoms each evening for 5 days in a diary and recorded use of paracetamol and adverse events. Investigator scored signs and symptoms on the day of diagnosis (Day 0) and on the second visit (Day 6)
Interventions	All participants received amoxicillin-clavulanic acid 625 mg three times a day for 5 days
	Tx - betamethasone 1 mg orally once daily for 5 days; N = 21
	C group – placebo for 5 days; N = 21
	Use of additional medication - analgesics permitted, paracetamol 1000 mg 6-hourly for pain as needed, other symptomatic relief med. (i.e. oral decongestants, antihistamines, and mucolytics) not permitted
Outcomes	**Primary outcome:** Improvement of symptoms from Day 0-6
	Secondary outcomes: i) percentage of participants with physical signs present or absent on Day 0-6
	ii) number of paracetamol tablets taken
	iii) adverse events
Notes	**Setting -** three primary health care sites in Republic of South Africa, 2003
	Drop-outs total - not described

Footnotes
CT scan: computed tomography scan; ITT: intention-to-treat; MPID: mean pain intensity difference; N: number
PRID: pain relief intensity difference; Tx: treatment; C: control

Appendix 3. Characteristics of excluded studies

Remer 2005	
Reason for exclusion	Chronic sinusitis

Ozturk 2011	
Reason for exclusion	Chronic sinusitis

Vaidyanathan 2011	
Reason for exclusion	Chronic sinusitis with nasal polyposis

Appendix 4. Characteristics of ongoing studies

Sachs APE, The Netherlands	
Study name	PRET (Prednisolone Rhinosinusitis Efficacy Trial) study
Methods	Double blind, placebo-controlled, randomised clinical trial
Participants	185 patients aged over 18 years with a clinical diagnosis of acute rhinosinusitis
Interventions	**Tx:** prednisolone 30 mg daily for 7 days **C group:** placebo All participants are allowed to take symptomatic relief medication (decongestive nose drops, paracetamol, and steam inhalation therapy)
Outcomes	**Primary outcome:** Proportions of patients with resolution of facial pain/pressure at Day 7 **Secondary outcomes:** i) Proportions of patients with resolution of other symptoms (separate and combined) at Day 7 ii) Time to resolution of symptoms iii) Median duration of symptoms iv) Health-related quality of life v) Resumption of daily activities (school/work)
Starting date	1 March 2008
Contact information	APE Sachs, Julius Center for Health Sciences and Primary Care, UMCU, The Netherlands
Notes	Trial registration: The Netherlands National Trial Register (NTR=1295)

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Chapter 4

Systemic corticosteroids for clinically diagnosed acute rhinosinusitis

A double blind, placebo-controlled, randomised clinical trial

Abstract

Background

Symptoms consistent with acute rhinosinusitis are a common reason for doctor consultations in general practice. Nowadays, paranasal mucosa inflammation is increasingly considered as the predominant path in the causation of its symptoms. Therefore, (intranasal) corticosteroids could be effective by attenuating of the host inflammatory response and relieving symptoms. Although frequently used in daily practice, evidence on their benefits is inconclusive. The aim of the present study was to determine the effectiveness of systemic corticosteroids in patients with clinically diagnosed ARS.

Methods

We performed a multicenter, double blind, placebo-controlled, randomised clinical trial with computer generated block randomisation between December 2008 and April 2011. A total of 68 general practitioners out of 54 general practices in the province Zeeland, recruited eligible patients during their daily practice. Participating general practices received sealed blind-sequenced trial containers in randomised blocks of four. Patients aged 18 years and older with clinically diagnosed ARS (defined as ≥ 2 diagnostic criteria: nasal discharge or nasal congestion and facial pain/pressure or pain when masticating) were assessed for eligibility. Participants were randomly allocated to either prednisolone 30 mg daily for 7 days or placebo. The primary outcome was the proportion of patients with resolution of facial pain/pressure at day 7. Secondary outcomes were time to resolution of symptoms, median duration of symptoms, and health related quality of life (HRQoL).

Results

185 patients (prednisolone n=93; placebo n=92) were randomised. Two participants withdrew from study and nine participants were excluded from primary analysis because of incomplete symptom reporting, leaving 174 (n=88; n=86) patients for intention-to-treat analysis. The proportions of patients with resolution of facial pain/pressure at day 7 were 55 out of 88 (62.5%) in the prednisolone group versus 48 out of 86 (55.8%) in the placebo group (RD 6.7%, 95% CI -7.9% to 21.2%). Imputation of the nine missing outcomes led to similar results (RD 7.1%, 95% CI -7.2% to 21.4%). The proportion of patients with decreased symptoms was similar in both groups. HRQoL did not differ between those in the prednisolone and those in the placebo group across the different time points. Adverse events reported were mild and did not differ between the groups.

Conclusion

Systemic corticosteroids appear to have no clinically relevant beneficial effects in patients with clinically diagnosed ARS.

Introduction

Acute rhinosinusitis (ARS) is a common reason for patients to visit a general practitioner (GP).[1 2] In general practice, the diagnosis is based on clinical signs and symptoms[3] since the additional diagnostic value of laboratory measurements and imaging techniques is either too low or tests are not cost-effective.[4-7]

Symptoms consistent with ARS are self-limiting in the majority of patients within a period of four weeks, but its unpleasant symptoms are associated with impaired daily functioning and can reduce the quality of life.[8] Patients may therefore seek medical attention in order to relieve symptoms and accelerate recovery. This, along with the belief that symptoms of ARS are caused by a bacterial infection, might explain the high antibiotic prescription rates in daily practice ranging from 70% in the Netherlands to approximately 90% in the United Kingdom and the United States.[1 2 9] Although antibiotics might be beneficial in a subgroup of patients in which the diagnosis is confirmed by computed tomography (CT) scan[10], current evidence indicates that the vast majority of patients with clinically diagnosed ARS in general practice do not benefit from antibiotics.[11] New treatment targets should therefore shift away from antibiotics in order to reduce unnecessary side-effects and antimicrobial resistance.

Nowadays, acute inflammation of the paranasal mucosa due to infectious (viruses, bacteria) and non-infectious (allergens, idiopathic triggers) causes is increasingly considered as the predominant path in the causation of symptoms in ARS.[12-15] Based on these pathophysiological considerations, anti-inflammatory drugs might be effective by attenuating the host inflammatory response. Consequently, intranasal corticosteroids (INCS) could be a treatment option in clinically diagnosed ARS. Current evidence on their benefits is, however, inconclusive.[16 17] Systemic administration of corticosteroids might have several advantages over INCS such as higher corticosteroid levels and a no risk of poor deliverance because of nasal blockage, and could therefore provide increased anti-inflammatory effects. A recent Cochrane review on systemic corticosteroids for ARS reported a short-term beneficial effect of systemic corticosteroids.[18] However, data were limited, almost all patients were recruited in secondary care, and all included studies did assess the effect of corticosteroids in addition to antibiotics. Consequently, additional trials were warranted to provide a more definite answer on the use of (systemic) corticosteroids in clinically diagnosed ARS.

The objective of our double blind, placebo-controlled, randomised clinical trial therefore was to study the effectiveness of systemic corticosteroids (prednisolone 30 mg daily for seven days) in adult patients who visited their GP with clinically diagnosed ARS for at least five days.

Methods

Trial design, setting and participants

We performed a multicenter, double blind, placebo-controlled, randomised clinical trial between December 2008 and April 2011. A total of 68 GPs out of 54 general practices in the province Zeeland, which is situated in the Southwest of the Netherlands, recruited eligible patients during their daily practice.

Patients were eligible to participate in the trial if they were aged 18 years and older, and had visited their GP with symptoms of uncomplicated ARS for at least five days and a maximum of twelve weeks. We used a clinical diagnosis for ARS which was in agreement with the definition of the European Position Paper on Rhinosinusitis and Nasal Polyps 2007.[3] Patients needed to have at least two symptoms: one of which had to be either nasal discharge (anterior/posterior nasal drip) or nasal congestion and one symptom had to be either facial/pain pressure or pain when masticating. We excluded patients with a complicated course of ARS (i.e. orbital swelling, fever ≥ 38.5 °C after five days of complaints) and patients with a history of recurrent rhinosinusitis (≥ 2 episodes of ARS in previous 12 months). Other exclusion criteria were: pregnancy, previous ear-nose-throat surgery for malignancy, contra-indication for prednisolone treatment and use of either intranasal or oral corticosteroids in the previous four weeks. Neither GPs nor patients did receive financial reimbursement for participating in the trial. The study was approved by the medical ethics committee of the University Medical Center (UMC) Utrecht and the central committee on research involving human subjects of the Netherlands.

Randomisation

After obtaining full-written informed consent, the GP randomly allocated enrolled participants to either prednisolone 30 mg daily for 7 days (treatment) or placebo for 7 days (control) using sealed blind-sequenced trial containers. The sealed blind-sequenced trial containers were only identifiable by the randomisation code number and were distributed to participating practices in randomised blocks of four. The corticosteroid and placebo drugs, manufactured by the pharmacy department of the UMC Utrecht (independent to trial team), were identical in taste and appearance. The block randomisation sequence was made by the pharmacy department of the UMC Utrecht using computer generated random numbers. The randomisation code was kept at a locker in the pharmacy department throughout the study period and was not broken until data collection was completed and blinded analyses had been performed.

Baseline and follow-up measurements

GPs completed a baseline questionnaire including (duration and severity of) symptoms, co-morbidities (i.e. (seasonal) allergic rhinitis, eczema and asthma) and consultation for ARS in the previous three years. Additionally, a basic physical examination was performed including temperature and anterior rhinoscopy.

Main study outcomes were obtained from a self-reported patient diary. Patients were instructed to record their symptoms and medication use in a 14-day symptom diary. This diary included questions regarding symptoms of asthma and (allergic) rhinitis in the previous year[19], the use of trial medication and/or symptomatic relief medication (i.e. paracetamol, decongestive nose drops), daily activities (work or school), and daily entries of seven symptom variables: (1) facial pain/pressure, (2) nasal congestion/blockage, (3) postnasal discharge, (4) runny nose (5) lack of a good night's sleep, (6) cough, (7) reduced productivity. Additionally, questions regarding disease specific health-related quality of life (HRQoL) were answered on day 1, 7 and 14 using the Sino-Nasal Outcome Test 20 (SNOT-20). This self-reported HRQoL questionnaire is developed and validated for patients with symptoms of rhinosinusitis and includes 20 items regarding physical, functional and emotional status.[20] [21] Both daily symptom variables and SNOT-20 questionnaire variables were scored as 0 for normal or no problem, 1 for very mild problem, 2 for mild or slight problem, 3 for moderate problem, 4 for severe problem, and 5 for problem as bad as it can be.

A blood sample was taken on voluntarily basis for C-reactive protein testing and the Phadiatop test, an allergen-specific IgE test to a panel of common aeroallergens in adults; its result was classified as positive or negative. Laboratory testing was performed by the clinical chemistry department of the local hospitals (Admiraal de Ruyter Ziekenhuis) and by SHL centre for Diagnostic Support in Primary Care. Patients were contacted by telephone at day 2 or 3 of the study by the coordinating investigator to provide answer to questions and to enhance compliance.

At day 14 of the study, patients returned to their GP for an evaluation of their symptoms and for handing over their diary and (empty) medication container. The GP was asked to perform a short physical examination and complete a questionnaire including a question whether the patients had consulted a physician in the last two weeks.

At the end of follow-up (= 8 weeks) GPs were asked to complete a questionnaire regarding patients' doctor consultations and medication use in the past 6 weeks and patients were contacted by telephone by the coordinating investigator to complete a questionnaire, including the SNOT-20 questionnaire.

Primary and secondary outcomes

The primary outcome measure was the proportion of patients with resolution of facial pain/pressure at day 7. Resolution of facial pain/pressure was defined as score 0 or 1 (no problem or very little problem combined).

Secondary outcomes were proportions of patients with resolution of severe facial pain/pressure (defined as absence of score 4 or 5) at day 7, proportions of patients with resolution of other clinically relevant symptoms (nasal congestion, postnasal discharge, cough, runny nose) at day 7, time to resolution of total symptoms (combining runny nose, nasal congestion, cough, postnasal discharge and facial pain), median duration of symptoms, HRQoL using the SNOT-20 questionnaire and resumption of daily activities.

Power and statistical analysis

Based on a previous trial in patients with signs and symptoms of ARS with similar entry criteria, the proportion with complete resolution of facial pain/pressure at day 7 in the placebo group was expected to be 50%.[22] To assess a (clinical relevant) difference of 20%[16], a minimum of 184 patients had to be included in the trial (α=0.05, β=0.20).

For dichotomous outcomes (e.g. proportions of patients with resolution of symptoms at day 7), risk differences (RDs), relative risks (RRs), and 95% confidence intervals (CIs) were calculated. Binomial logistic regression analyses with a robust covariance matrix estimator were used to adjust for differences in baseline characteristics (potential confounders). Differences in median duration of symptoms were calculated. We used Mann-Whitney U tests to evaluate differences between the groups. HRQoL was calculated by combining individual scores of all items of the SNOT-20 questionnaire to a total score (ranging from 0 to 100). Mean SNOT-20 scores for both groups were presented for baseline, day 7, day 14 and week 8. We used Student's t-tests to evaluate differences between the two groups. Proportions of patients with resumption of daily activities were calculated.

In post-hoc analyses, potential modification of the effect of corticosteroids on day 7 was evaluated with binomial logistic regression analyses including interaction terms for atopic status (Phadiatop test positive versus negative), (seasonal) allergic rhinitis (yes versus no), nasal symptoms - such as sneezing, runny nose or nasal congestion - when not having the flu or a cold for at least 3 months per year (yes versus no), recurrent sinusitis (History of sinusitis in previous 3 years yes versus no), duration of symptoms prior to randomisation (≤ 14 days versus > 14 days) and baseline severity of symptoms (3 out of 5 symptoms severe yes versus no). Subgroups were only presented in case of significant interaction effects.

We also performed two sensitivity analyses: an analysis in which we imputed the missing data using multiple imputation23 and an analysis in which we changed the

definition of resolution of total symptoms (secondary outcome measure) from resolution of all symptoms into resolution of 80% of symptoms (four out of five) and resolution of 60% of symptoms (three out of five). All analyses were performed according to the intention-to-treat principle, using SPSS version 17 (SPSS Inc., Chicago, Illinois) and Rothman's Episheet version June 11, 2008 (http://www.drugepi.info/links/downloads/episheet.xls).

Results

Participants

Between December 2008 and April 2011, a total of 218 patients were assessed for eligibility by their GP. Of them, 33 were excluded for various reasons and 185 were randomised: 93 to prednisolone and 92 to placebo (Figure 1). Baseline characteristics are shown in Table 1. Mean age was 43.9 years in the prednisolone group versus 42.4 years in the placebo group and median duration of symptoms prior to randomisation was 12 and 13.5 days, respectively. Except for gender and atopic status (Phadiatop test) there were no clinically relevant differences in baseline characteristics between the prednisolone and the placebo group (Table 1). In both groups, one patient withdrew from study at day 1. From the remaining 183 patients, a total of nine patients (4.9%) were excluded from analysis due to missing data for primary outcome, leaving 174 patients (prednisolone= 88 and placebo=86) for primary analysis (Figure 1).

Figure 1. Flow diagram
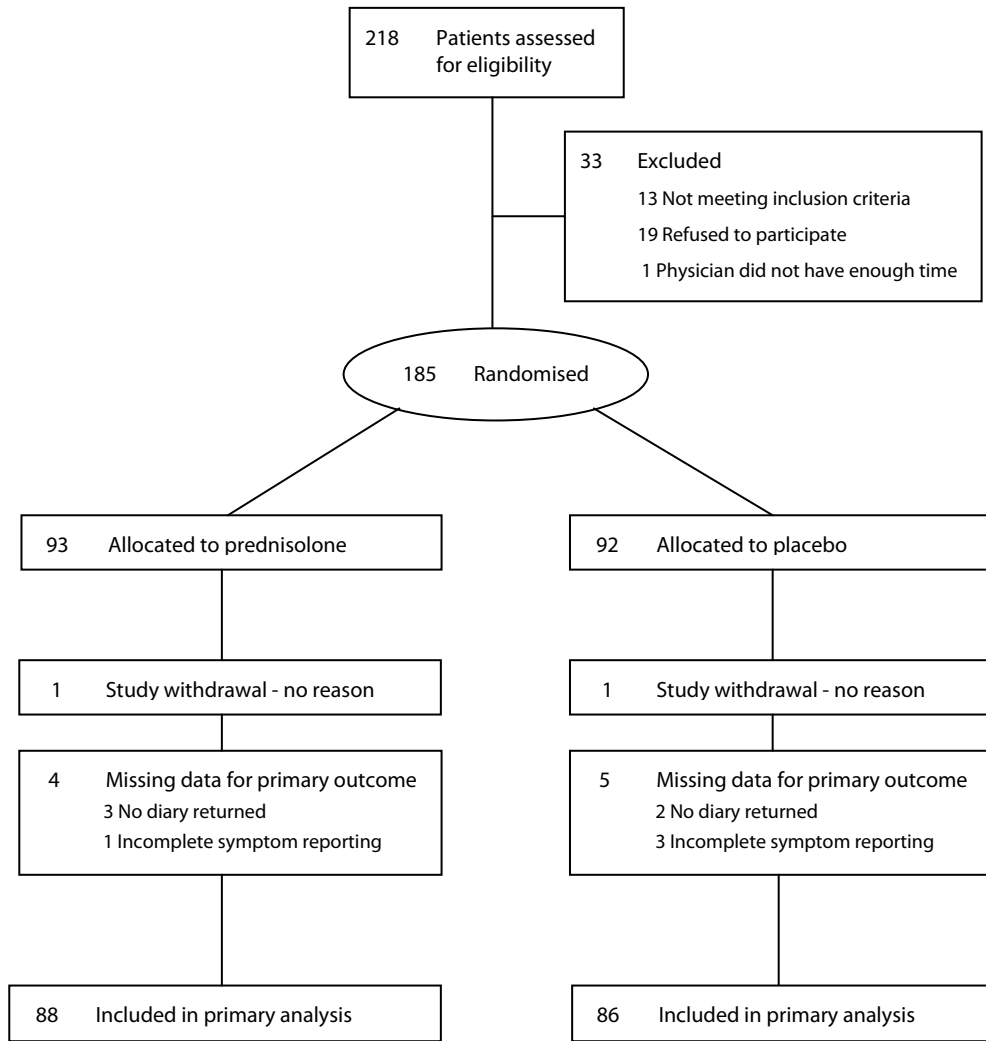
Table 1. Baseline characteristics

	Prednisolone (n=93)	Placebo (n=92)
Patient characteristics		
Age, mean (SD)	43.9 (13.6)	42.4 (13.7)
Gender, female (%)	63 (67.7)	51 (55.4)
Smoking history		
Never	34 (38.2)	37 (41.6)
Past	30 (33.7)	35 (39.3)
Current	25 (28.1)	17 (19.1)
Recent history of rhinosinusitis*	30 (32.6)	29 (32.2)
Asthma (%)	6 (6.5)	8 (8.8)
(Seasonal) allergic rhinitis (%)	18 (19.6)	16 (18.0)
Eczema (%)	6 (6.5)	8 (8.9)
Chronic obstructive pulmonary disease (%)	1 (1.1)	1 (1.1)
Disease characteristics		
Duration of symptoms, median (IQR)	12 (7-20)	13.5 (7-21)
Initial temperature, median (IQR), °C	36.7 (36.3-37.0)	36.7 (36.3-37.0)
Pus on inspection (%)	19 (20.4)	19 (20.9)
Postnasal drip on inspection (%)	17 (19.3)	15 (16.7)
Nasal congestion (%)	78 (83.9)	78 (84.8)
Facial pain/pressure (%)	89 (95.7)	88 (95.7)
Unilateral (%)	27 (36.5)	30 (39.5)
Bilateral (%)	47 (63.5)	46 (60.5)
Severity of facial pain, mean (SD) #	3.0 (1.3)	3.1 (1.4)
Severity of problem according to doctor		
Little problem	26 (28.0)	27 (30.3)
Moderate problem	63 (67.7)	61 (68.5)
Severe problem	4 (4.3)	1 (1.1)
Laboratory measurements		
C-Reactive protein, median (IQR)	5.2 (2.3-14.7)	8.2 (1.0-22.0)
Phadiatop test positive (atopic status) (%)	29 (35.4)	21 (27.3)

* Recent history of rhinosinusitis is defined as doctor consultation for rhinosinusitis in previous three years

Severity of facial pain on baseline (day 1) as scored by patient (0=no problem, 1=very mild problem, 2=mild problem, 3=moderate problem, 4= severe problem, 5 = problem as bad as it can be)

Primary and secondary outcomes

The proportions of patients with resolution of facial pain/pressure at day 7 were 55 out of 88 (62.5%) in the prednisolone group versus 48 out of 86 (55.8%) in the placebo group (RD 6.7%, 95% CI -7.9% to 21.2%) (Table 2). Imputation of the nine missing outcomes led to similar results (RD 7.1%, 95% CI -7.2% to 21.4%).

Results on other clinically relevant symptoms, either separate or combined (total symptoms), were in concordance with the findings for facial pain, except for the proportion of patients with resolution of severe facial pain/pressure at day 7 which was higher among those receiving prednisolone (RD 10.6%, 95% CI 1.0 to 20.2). Median duration of facial pain was 4.5 days (IQR 2-8) in the prednisolone group and 5 days (IQR 2-9) in the placebo group, resulting in a difference of 0.5 days (p=0.82) (Table 2). Analysis of total symptoms revealed a difference of two days in favour of prednisolone (9 versus 7 days respectively, p=0.17). The decrease of symptoms over time was similar in both groups (Figure 2). HRQoL did not significantly differ between those in the prednisolone and those in the placebo group across the different time points. Resumption of daily activities (work / school) over time was comparable in both groups.

Binomial logistic regression analyses to adjust for gender and atopic status (Phadiatop test) revealed similar effect estimates as the unadjusted analyses.

Subgroup analyses

No statistically significant interaction effects were found regarding atopic status, (seasonal) allergic rhinitis, recurrent rhinosinusitis, chronic nasal symptoms, duration of symptoms prior to randomisation and baseline severity.

Table 2. Main study outcomes – Proportions of patients with resolution of symptoms at day 7

	Prednisolone	Placebo	RD (95% CI)	RR (95% CI)
Primary outcome				
Facial pain	55/88 (62.5%)	48/86 (55.8%)	6.7% (-7.9 to 21.2)	1.12 (0.87 to 1.44)
Secondary outcomes				
Severe facial pain [#]	82/88 (93.2%)	71/86 (82.6%)	10.6% (1.0 to 20.2)	1.13 (1.01 to 1.26)
Nasal congestion	50/87 (57.5%)	46/86 (53.5%)	4.0% (-10.8 to 18.8)	1.07 (0.82 to 1.40)
Postnasal discharge	48/88 (54.5%)	49/85 (57.6%)	-3.1% (-17.9 to 11.7)	0.95 (0.73 to 1.23)
Runny nose	61/88 (69.3%)	50/86 (58.1%)	11.2% (-3.0 to 25.3)	1.19 (0.95 to 1.50)
Cough	57/86 (66.3%)	46/84 (54.8%)	11.5% (-3.1 to 26.1)	1.21 (0.95 to 1.55)
Total Symptoms [*]	28/85 (32.9%)	21/83 (25.3%)	7.6% (-6.1 to 21.3)	1.30 (0.81 to 2.10)
Severe total symptoms	69/85 (81.2%)	65/83 (78.3%)	2.9% (-9.3 to 15.0)	1.04 (0.89 to 1.21)
Sensitivity analysis				
Total Symptoms_4 out of 5	38/85 (44.7%)	33/83 (39.8%)	5.0% (-10.0 to 19.9)	1.12 (0.79 to 1.60)
Total Symptoms_3 out of 5	53/85 (62.4%)	48/83 (57.8%)	4.5% (-10.3 to 19.3)	1.08 (0.84 to 1.38)
Median duration in days (IQR)			Difference	p-value ^
Facial pain	4.5 (2-8)	5 (2-9)	0.5	0.819
Nasal congestion	4 (2-7)	4 (2-9)	0	0.763
Postnasal discharge	3.5 (1-8)	3 (1-8)	-0.5	0.658
Runny nose	2 (2-4)	1 (1-8)	1	0.464
Cough	2 (1-5)	3 (1-8)	1	0.046
Total Symptoms [*]	7 (4-14+)	9 (6-14+)	2	0.170
Total Symptoms_4 out of 5	5 (3-8)	6 (3-11)	1	0.129
Total Symptoms_3 out of 5	3 (2-5)	4 (2-7)	1	0.155

RD = absolute risk difference, RR = relative risk, CI = confidence interval, n/a = not applicable

Resolution of symptoms is defined as symptom score 0 (normal, no problem) and score 1 (very mild problem)

[#] Resolution of severe facial pain is defined as absence of severe pain (score 4 or 5) at day 7

[*] Total symptoms: complete relief of runny nose, postnasal discharge, nasal congestion, cough and facial pain

^ Differences between groups based on Mann-Whitney U tests (p-values)

Figure 2. Proportions of patients with symptoms over time

Total symptoms over time

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Week 8
prednisolone	98,8%	93,2%	88,6%	79,3%	77,1%	71,1%	67,1%	57,8%	63,9%	55,1%	49,4%	43,5%	42,5%	43,5%	53,4%
placebo	98,9%	97,7%	92,9%	89,3%	82,1%	75,9%	74,7%	66,7%	58,8%	57,1%	51,8%	42,9%	35,4%	39,5%	43,5%
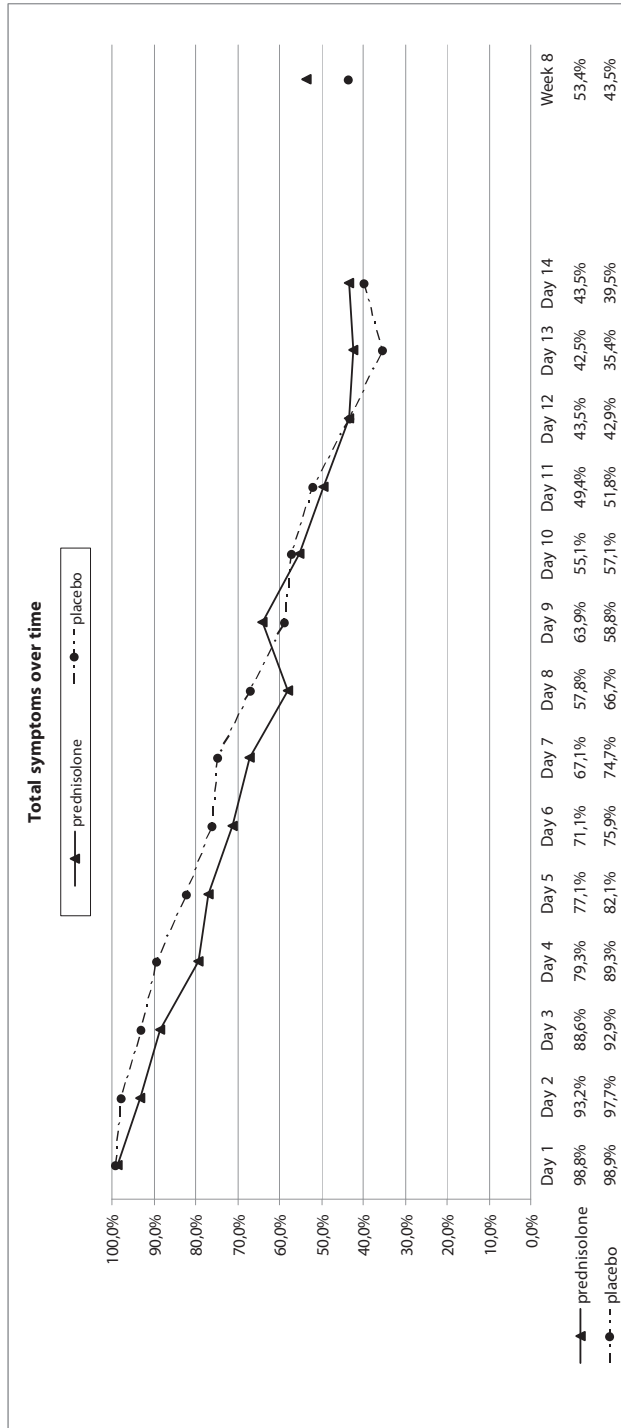
Total symptoms: combined symptoms of runny nose, postnasal discharge, nasal congestion, cough and facial pain

Follow-up

The proportions of patients with resolution of facial pain and total symptoms at eight weeks was higher among those receiving placebo, though the difference was not statistically significant (RD -2.2%, 95% CI -12.6% to 8.1% and RD -9.9%, 95% CI -24.7% to 4.9%, respectively) (Figure 1).

During eight weeks of follow-up, no significant differences in consultation rates for (persistent) symptoms of ARS were observed between the prednisolone group (18 out of 88) and the placebo group (21 out of 86). Additionally, antibiotic prescription rates were similar in both groups: 17 out of 88 versus 16 out of 86, respectively. Participants that received antibiotics had more frequently a negative Phadiatop test, and the duration of symptoms prior to randomisation was significantly longer as compared to participants that did not receive antibiotics.

During follow-up, INCS prescription rates were comparable: 16 out of 88 and 15 out of 86, respectively. Participants that received INCS had more frequently pus in the nasal cavity at baseline examination, had more often a recent history of ARS (GP visit in previous three years), and had longer duration of symptoms prior to randomisation as compared to participants that did not receive INCS.

Adverse events

During the trial, two non drug-related serious adverse events were reported which were no reason for unblinding of these individual participants. Adverse events reported were mild (i.e. gastric complaints, increased appetite, mood and sleep disturbance) and did not differ between the groups (Table 3).

Table 3. Adverse events

	Prednisolone	Placebo	p-value *
Day 7			
Gastric complaints	11	8	0.50
Diarrhea	14	10	0.40
Increased appetite	14	7	0.13
Mood disturbance	13	15	0.73
Sleep disturbance	24	28	0.54
Day 14			
Gastric complaints	7	5	0.59
Diarrhea	12	8	0.36
Increased appetite	8	3	0.13
Mood disturbance	9	11	0.56
Sleep disturbance	12	15	0.49

* Pearson's Chi-square test

Discussion

Summary of main findings

No clinically relevant differences in outcome were observed in patients with clinically diagnosed ARS receiving prednisolone or placebo. Subgroup analyses revealed no significant interaction effects. Adverse events reported were mild and did not differ between the groups.

Strengths

To our knowledge, this is the first double blind, placebo-controlled, randomised clinical trial on the effectiveness of systemic corticosteroids as a monotherapy in patients with clinically diagnosed ARS. Only two participants withdrew from the study, while the number of missing data on primary outcome in our study was below five percent.

Our intervention, i.e. prednisolone 30 mg for 7 days, is a widely and successfully used treatment regimen for respiratory tract diseases with a major inflammatory component and a relative acute onset of symptoms such as exacerbations of asthma and chronic obstructive pulmonary disease.[24][25] Consequently, it should have been able to provide sufficient anti-inflammatory effects for answering the question whether cortico-steroids are effective in patients with clinically diagnosed ARS. Moreover, the use of higher dosage of prednisolone (>40 mg daily) is associated with an increase in (psychiatric) side-effects, which would be highly undesirable in a relatively mild self-limiting condition such as acute rhinosinusitis.[26][27]

Limitations

Before drawing conclusions from these findings, there are some potential limitations that deserve further discussion. We used a clinical diagnosis of ARS rather than radiological assessment (e.g sinus X-ray or CT scanning) prior to randomisation, and some of our patients might therefore not have had radiological evidence of rhinosinusitis. Previous meta-analyses on the effects of antibiotics in ARS have demonstrated that the use of radiological assessment as part of the inclusion criteria lead to different results as compared to clinical diagnosis alone.[11][28] However, almost all patients with ARS are seen in general practice and radiological imaging is not routinely performed in this setting prior to treatment decision. Inclusion based on radiological assessment would therefore have strongly reduced the generalisability of our findings. Moreover, our definition of ARS is in agreement with the definition of the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 [3], and our study population is comparable with those in other relevant studies on ARS in general practice.[16][17][22] Our findings are therefore representative for the broad population of patients with clinically diagnosed ARS that are encountered in general practice.

Our primary analysis was based on complete-outcome assessment (complete case analysis) because of the low number of missing data on our primary outcome (4.9%). However, missing data rarely occur completely at random and complete case analysis might lead to loss of statistical power and biased results.[29] We therefore performed sensitivity analysis by imputing missing data based on the multiple imputation method. Results of this sensitivity analysis did not differ from our primary analysis which supports the validity and precision of our findings.

Our study was underpowered to detect statistical significant differences in subgroup analyses. Although no statistical significant interaction effect was found, post-hoc subgroup analysis of patients with chronic nasal symptoms throughout the year (three months or more) revealed a strong trend towards beneficial effects of corticosteroids. In addition, we excluded patients who used INCS in the previous four weeks. Based on the current evidence on the efficacy of INCS in (non)allergic rhinitis, ARS patients with this underlying condition might benefit from corticosteroids. Further research is needed to determine the effectiveness of (intranasal) corticosteroids in the subgroup of patients with clinically diagnosed ARS and underlying (non)allergic rhinitis and/or chronic nasal symptoms.

Comparison with existing literature

A recent systematic review and meta-analysis of four studies on systemic cortico-steroids as adjunctive therapy to oral antibiotics revealed short-term beneficial effect in patients with ARS as compared to control treatment (placebo or NSAIDs).[18] However, the methodological quality of the included studies were judged moderate and the independent effect of corticosteroids could not be determined as all included studied used oral antibiotics as co-treatment. Moreover, three of the four included studies were performed in secondary care settings and used radiological assessment as part of the inclusion criteria.

A recent systematic review and meta-analysis of studies on INCS with or without antibiotics for ARS as confirmed by radiological assessment or nasal endoscopy demonstrated a very modest beneficial effect (for every 100 patients treated with INCS, seven additional patients had complete or marked symptom relief at 15 to 21 days; NNT=15).[30] Moreover, a subsequent trial on INCS as a monotherapy for clinically diagnosed ARS reported no beneficial effect.[16] It was, however, unknown whether these findings could be explained by the poor delivery of INCS due to blocked nasal passages or by the lack of anti-inflammatory effect in ARS. The results of our study indicate that these findings are probably due to a real lack of anti-inflammatory effects of corticosteroids in the broad population of patients with clinically diagnosed ARS.

Implications for clinical practice

As no clinically relevant effects of systemic corticosteroids were observed, we conclude that there is no rationale for using anti-inflammatory agents in the broad population of patients with clinically diagnosed ARS. Future studies should focus on identifying subgroups among the heterogeneous population of clinically diagnosed ARS that would benefit from antibiotics or (intranasal) corticosteroids. Unless the efficacy of such tailored treatment regimens have been confirmed, we strongly recommend physicians to refrain from treatment with antibiotics and (intranasal) corticosteroids and advocate symptomatic treatment (decongestive nose drops, analgesics) in patients with clinically diagnosed ARS.

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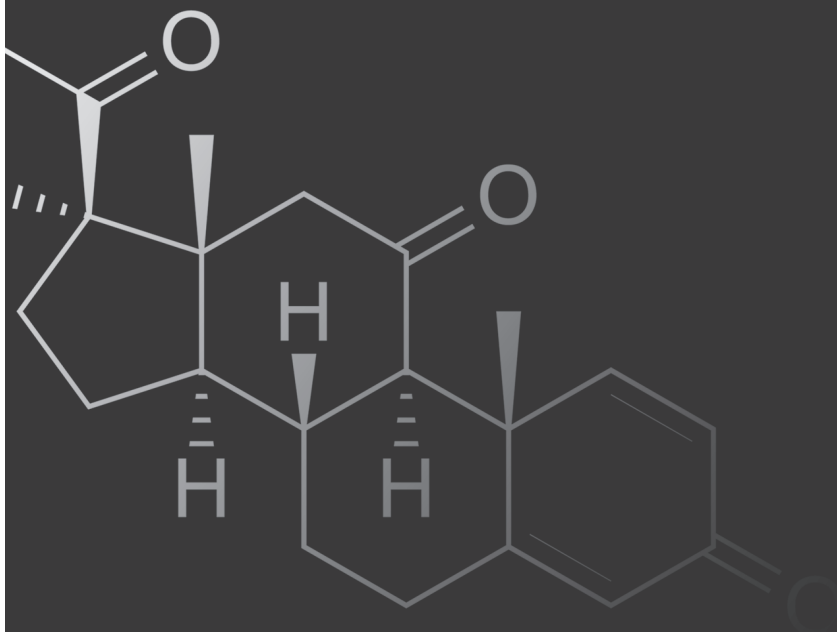
Chapter 5

Reporting subgroup analysis in randomised controlled trials

Abstract

Background

Subgroup analyses are increasingly performed in randomised controlled trials (RCTs). Although reporting of both relative (e.g. relative risk (RR), odds ratio (OR), hazard ratio (HR)) and absolute (e.g. risk difference (RD)) effect measures for primary and secondary outcomes in RCTs is strongly advocated by the CONSORT statement, no clear recommendations on the use of specific effect measures for subgroup analyses exist. Subgroup results can, however, differ depending on whether relative or absolute effect measures are used. The objectives of the current study are to assess whether relative or absolute effect measures were used in subgroup analyses of RCTs, and whether these subgroup effect measures differed from the main effect measures. We also studied whether conclusions would change if subgroup effects were calculated on a different scale than reported.

Methods

We studied all RCTs (n=327) published in 2010 in five major general medical journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet and New England Journal of Medicine). For trials with a dichotomous primary outcome, we extracted the reported effect measures for both the main and subgroup effects. If crude data of subgroups were reported, we calculated subgroup effects on both a relative and an absolute scale.

Results

Of the 229 RCTs with a dichotomous primary outcome, 120 (52%) performed subgroup analyses. In 106 of these 120 RCTs (88%), relative effect measures were used for subgroup analyses, whereas subgroup effects were presented on an absolute scale in nine trials (8%). Two RCTs (2%) reported both relative and absolute subgroup effects. Most of the 120 trials (74%) reported the same effect measure for the main and subgroup effect. However, eight trials (7%) that used an absolute effect measure for the main effect (RD) assessed subgroup effects on a relative scale (OR, HR). We were able to extract crude data of subgroups in 61 of the 120 RCTs (51%). Calculating subgroup effects on a different scale then reported lead to a change in conclusion in one out of five trials.

Conclusions and recommendation

Almost all RCTs used relative effect measures for subgroup analyses. Interpretation of subgroup effects appeared to be dependent on whether relative or absolute effect measures were used. Reporting of relative risk reduction should therefore always be accompanied by presenting the absolute risk reduction. The CONSORT statement should incorporate such recommendations not only for primary and secondary outcomes but also for subgroup analyses.

Introduction

Randomised controlled trials (RCTs) are widely regarded as providing the most reliable evidence on the benefits and harms of interventions. In addition to main analyses, RCTs often perform subgroup analyses to identify specific subgroups of patients that do (or do not) benefit from the intervention.[1-3] Clinical guidelines increasingly incorporate results of subgroup analyses and such findings can therefore influence clinical decisions considerably.

Previous studies demonstrated that interpretation of trial results may be influenced by the use of either relative (e.g. relative risk (RR), odds ratio (OR), hazard ratio (HR)) or absolute (e.g. risk difference (RD)) effect measures in outcome reporting as benefits of interventions are often perceived larger if outcomes were reported with relative effect measures than if the same trial results were presented with absolute effect measures.[4-8] Consequently, reporting both relative and absolute effect measures for primary and secondary outcomes in RCTs is, nowadays, strongly recommended by the Consolidated Standards of Reporting Trials (CONSORT) statement.[9] Opposite to these explicit recommendations for the main analyses, the current CONSORT statement does not include clear recommendations on the use of specific effect measures for subgroup analyses. This, however, is remarkable as it has been acknowledged that subgroup analyses can lead to different results and conclusions with regard to statistical significance depending on whether relative or absolute effect measures are used.[10] To illustrate this phenomenon, we provide numerical examples based on RCTs performed by Dondorp et al.[11] (Box 1) and by Decousus et al.[12] (Box 2).

As far as we are aware no previous studies have been performed to investigate whether subgroup analyses are reported with relative or absolute effect measures, and what the impact of such choices may be. We therefore systematically reviewed RCTs that were published in five major general medical journals to assess whether relative or absolute effect measures were used in subgroup analyses, and whether these subgroup effect measures differed from the main effect measures. We also studied whether conclusions would change if subgroup effects were calculated on a different scale than reported.

Box 1. Numerical example based on Dondorp et al. [11]

In this randomised controlled trial children (<15 years) with severe falciparum malaria were randomly assigned to either parenteral artesunate (n=2712) or quinine (n=2713). The primary outcome was in-hospital mortality (measure of effect: OR). In the treatment group (artesunate) 230 patients (8.5%) died in the hospital compared with 297 patients (10.9%) in the control group (quinine). This results in the following table:

	Artesunate	Quinine	OR (95% CI)	RR (95% CI)	RD (95% CI)
Primary outcome In-hospital mortality	230/2712 (8.5%)	297/2713 (10.9%)	0.75 (0.63 to 0.91) p=0.002	0.77 (0.66 to 0.91) p=0.002	-2.5% (-4.0 to -0.9) p=0.002

The authors performed nine prespecified subgroup analyses (measure of effect: ORs) including the presence or absence of acidosis (defined as base excess ≤ 8 mmol/L). The crude numbers of the subgroup analyses were presented in figure 3 of the article. Based on these numbers, the ratio of ORs, RRs and the difference in RDs across both strata can be calculated, resulting in the following table:

	Artesunate	Quinine	OR* (95% CI)	RR (95% CI)	RD (95% CI)	Ratio of ORs (95% CI)	Ratio of RRs (95% CI)	Diff. of RDs (95% CI)
Acidosis – no In-hospital mortality	49/1275 (3.8%)	52/1314 (4.0%)	0.97 (0.65 to 1.44)	0.97 (0.66 to 1.42)	-0.1% (-1.6 to 1.4)			
Acidosis – yes In-hospital mortality	149/1009 (14.8%)	189/975 (19.4%)	0.72 (0.57 to 0.91)	0.76 (0.63 to 0.93)	-4.6% (-7.9 to -1.3)	1.35 (0.85 to 2.14) p=0.21	1.27 (0.83 to 1.96) p=0.27	4.5% (0.9 to 8.1) p=0.02

Conclusion: it depends on the scale of subgroup analysis whether the treatment effect differs among the subgroup, i.e. statistically significant difference on absolute scale (difference of RDs) and a non-statistical significant difference on relative scale (ratio of ORs and ratio of RRs).

Legend

OR: Odds Ratio, RR: Relative risk, RD: Risk Difference, CI: Confidence Interval

*The ORs reported in figure 3 of the article are slightly different from our calculated ORs due to stratification for study site

Box 2. Numerical example based on Decousus et al. [12]

In this randomised controlled adult patients (< 18 years) with acute, symptomatic lower-limb superficial-vein thrombosis were randomly assigned to either fondaparinux (n=1502) or placebo (n=1500). The primary outcome was a composite of death from any cause or symptomatic pulmonary embolism, symptomatic deep-vein thrombosis, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis at day 47.

The authors performed 16 prespecified subgroup analyses including the distance of thrombus from saphenofemoral junction (<10 cm or ≥10 cm). The measure of effect for these subgroup analyses was HR. Only (percentages of) events and absolute numbers of patients across 12 subgroups were presented in figure 2 of the article (i.e. they did not report person-time of follow-up across the subgroups). Based on these numbers, the ratio of RRs and the difference in RDs across both strata can be calculated, resulting in the following table:

	Fondaparinux	Placebo	HR * (95% CI)	RR (95% CI)	RD (95% CI)	Ratio of RRs (95% CI)	Diff. of RDs (95% CI)
Distance, <10 cm Composite primary outcome	1/117 (0.9%)	17/119 (14.3%)	0.06 (0.01 to 0.44)	0.06 (0.01 to 0.44)	-13.4% (-19.9 to -6.9)		
Distance, ≥10 cm Composite primary outcome	11/1235 (0.9%)	62/1235 (5.0%)	0.18 (0.09 to 0.34)	0.18 (0.09 to 0.34)	-4.1% (-5.5 to -2.8)	0.34 (0.04 to 2.75) p=0.31	-9.3% (-15.9 to -2.7) p=0.006

Conclusion: Although non-statistically significant on a relative scale (ratio of RRs), the absolute subgroup effect appears to be statistically significant with a large treatment effect (difference of RDs: -9.3%, 95% CI: -15.9% to -2.7%)

Legend

RR: Relative risk, RD: Risk Difference, CI: Confidence Interval

* The HR as reported in figure 2 of the article

Methods

Selection of trials

We included all RCTs that were published in 2010 in five major general medical journals: Annals of Internal Medicine (AIM), British Medical Journal (BMJ), Journal of the American Medical Association (JAMA), Lancet and New England Journal of Medicine (NEJM). These RCTs were retrieved by using a search filter for PubMed which combined the journal names with publication date [pd] '2010' and publication type [pt] 'randomized controlled trials' (Figure 1: Flowchart). We included all RCTs irrespective of design (e.g. parallel, factorial, crossover), study type (e.g. superiority, equivalence, non-inferiority), method of randomisation, or sample size. Trials that were published online in 2010 but on paper in 2011 were excluded. We also excluded research letters, cost-effectiveness analyses (CEAs), diagnostic accuracy studies, studies that were not RCTs and secondary analyses of RCTs.

Data extraction

We used a standardised data extraction form to assess the RCTs. This data extraction form was designed based on the five RCTs that were published on paper in 2011. Two reviewers (RV, MK) independently extracted data from the included trials. Discrepancies between the reviewers were resolved by discussion. For trials with a dichotomous primary outcome, we extracted the reported effect measure for the main effect (RR, OR, HR, incidence rate ratio (IRR), RD, incidence rate difference (IRD)), and determined whether results were statistically significant (p-value ≤ 0.05). Additionally, we assessed whether these RCTs performed subgroup analysis by reviewing the methods and results sections (including tables and supplementary appendix) of these trials. If so, we investigated the number of subgroup analyses performed, and whether relative or absolute effect measures (or both) were used. If possible, we extracted the crude data of the different subgroups to determine whether results and conclusions would change.

Data analysis

Frequencies and summary statistics of the extracted items were calculated. We used SPSS version 17 (SPSS Inc., Chicago, Illinois) for these analyses. If crude data of subgroups with two categories were reported, we calculated subgroup effects on both a relative (ratio of RRs or ratio of IRRs across strata and 95% confidence interval (CI) and p-value) and an absolute (difference of RDs or difference of IRDs across the subgroup strata and 95% CI and p-value) scale.[13] For further explanation of these calculations: see numerical example based on Dondorp et al.[11] (Box 1). For trials that used HRs as effect measure for the subgroup analyses, and which reported only events and absolute numbers of patients

across subgroups with two categories (i.e. they did not report person-time of follow-up across the subgroups), we calculated the RR and the RD of both subgroup strata. Additionally, we calculated both the ratio of RRs and the difference of RDs across strata with their 95% CIs and p-values. For further explanation of these calculations: see numerical example based on Decousus *et al.*[12] (Box 2). For subgroups with more than two categories, we used Rothman's Episheet version June 11, 2008 (http://www.drugepi.info/links/downloads/episheet.xls) to derive the p-value of the Mantel-Haenszel test for homogeneity for both relative and absolute scale. A change in conclusion was defined as a difference between relative and absolute subgroup effects with regard to statistical significance (p-value ≤ 0.05) in one or more subgroups of the included RCTs.

Results

Characteristics of included trials

We retrieved a total of 361 records from our initial search, of which 327 were eligible for our analyses (Figure 1). Most RCTs were published in NEJM (n=124, 38%), followed by Lancet (n=84, 26%), BMJ (n=49, 15%), JAMA (n=47, 14%) and AIM (n=23, 7%). The majority of RCTs investigated the effect of medication (61%), followed by surgical (10%) and behavioral interventions (9%). The median sample size of the RCTs was 499, ranging from 13 to 207,781 patients. A dichotomous primary outcome was reported in 229 trials. We excluded 109 trials with a dichotomous primary outcome that did not perform subgroup analysis, leaving 120 RCTs for further analysis (Figure 1).

Subgroup analysis

Subgroup analyses were more likely to be reported in trials without statistically significant main effects as compared to trials with statistically significant main effects (p=0.04). Subgroup effects were reported on a relative scale in 106 of the 120 RCTs (88%), whereas nine trials (8%) presented subgroup effects on an absolute scale (Table 1). Two trials (2%) used both relative and absolute effect measures for subgroup analyses. The majority of RCTs (74%) reported the same effect measure for the main and subgroup effect. However, eight trials (7%) that used an absolute effect measure (RD) for main effect used a relative scale for their subgroup effects. Most trals in which the effect measures for main and subgroup effects differed used ORs to report their subgroup effects.

Figure 1. Flowchart

Search PubMed
("N Engl J Med"[Journal] OR "JAMA"[Journal] OR "BMJ"[Journal] OR "Br Med J"[Journal] OR "Lancet"[Journal] OR "Ann Intern Med"[Journal]) AND 2010[dp] AND Randomized Controlled Trial[pt]

TOTAL
N = 361

Exclusion of articles that were published online in 2010 but on paper in 2011 (n=5)

N = 356

Articles excluded (n=17)
➤ Letters (n=5)
➤ CEA (n=4)
➤ Cohort study (n=2)
➤ Other (n=6)

N = 339

Exclusion of secondary analyses of RCTs (n=12)

N = 327

Exclusion of RCTs with non-dichotomous primary outcome (n=98)

N = 229

Exclusion of RCTs in which no subgroup analysis was performed (n=109)

N = 120

Table 1. Reported effect measures for main and subgroup effects

	Main effect (%)	Subgroup effect (%) ^
Absolute scale	**14 (12)**	**9 (8)**
Risk difference	13 (11)	8 (7)
Incidence rate difference	1 (1)	1 (1)
Relative scale	**84 (70)**	**106 (88)**
Relative risk	19 (16)	19 (16)
Odds ratio	11 (9)	24 (20)
Hazard ratio	53 (44)	62 (52)
Relative probability	1 (1)	1 (1)
Both relative and absolute scale	**18 (15)**	**2 (2)**
No measure of effect	**4 (3)**	**3 (3)**
TOTAL	**120 (100)**	**120 (100)**

Difference in effect measures between main and subgroup effects

Main effect	Subgroup effect	Frequency (%) ^
Absolute scale	**Relative scale**	**8 (7)**
Risk difference	Odds ratio	6 (5)
Risk difference	Hazard ratio	2 (2)
Relative scale	**Relative scale**	**5 (4)**
Relative risk	Odds ratio	3 (3)
Odds ratio	Hazard ratio	1 (1)
Hazard ratio	Relative risk	1 (1)
Both relative and absolute scale	**Relative scale**	**12 (10)**
Both relative and absolute scale	**Absolute scale**	**3 (3)**
Both relative and absolute scale	**No effect measure**	**1 (1)**
No effect measure	**Relative scale**	**2 (2)**
No effect measure	Odds ratio	2 (2)
No difference in effect measure		**89 (74)**

^ Percentages do not sum to 100 due to rounding

Absolute versus relative scale

In 59 of the 120 trials (49%), no subgroup data were presented (Table 2). Crude sub-grouping data could be extracted in 41 trials (34%), while 20 RCTs (17%) that used HRs as measure of effect for subgroup analyses reported only events and absolute number of patients across subgroups (i.e. they did not report person-time of follow-up across the subgroups).

Of the 41 trials from whom subgroup data could be extracted, 34 (83%) revealed similar subgroup effects on a relative and absolute scale regarding statistical significance (Table 2). In seven trials (17%) the subgroup effects differed regarding statistical significance when using a relative or absolute effect measure. For five of these seven RCTs (71%), the calculations revealed a non statistical significant subgroup effect on a relative scale and a statistically significant result on an absolute scale.

In 15 of the 20 trials (75%) that used HR as measure of effect for subgroup analysis and whom did not report person-time of follow-up across subgroups, relative and absolute subgroup effects were similar with regard to statistical significance (Table 2). In five trials (25%), the subgroup effects revealed a statistically significant result on an absolute scale but not on a relative scale.

Table 2. Subgroup analyses on relative and absolute scale based on crude data of 120 trials

	No data available (%)	Crude data (%)	HR (%) #	Crude data and HR (%) ^
Change in conclusion *	**n/a**	**7 (17)**	**5 (25)**	**12 (20)**
Stat. sign. relative scale AND Non-stat. sign. absolute scale	n/a	2 (5)	0 (0)	2 (3)
Non-stat. sign. relative scale AND Stat sign absolute scale	n/a	5 (12)	5 (25)	10 (16)
No difference	**n/a**	**34 (83)**	**15 (75)**	**49 (80)**
TOTAL	**59 (100)**	**41 (100)**	**20 (100)**	**61 (100)**

Stat. sign. = Statistical significance

^ Percentages do not sum to 100 due to rounding

HR: These RCTs used HRs as measure of effect for subgroup analyses and reported only events and absolute number of patients across subgroups (i.e. they did not report person-time of follow-up across the subgroups). For these trials we calculated relative subgroup effect as the ratio of relative risks (RRs) and absolute subgroup effect as the difference of risk differences (RDs) (see numerical example based on Decousus et al. [12] Appendix 2).

* Change in conclusion: it depends on the scale of subgroup analysis whether there is statistical significant heterogeneity of treatment effect among the subgroup (Appendix 1 and Appendix 2). Appendix 1 describes a numerical example of calculations with crude data of the RCT of Donders et al. [11] in which there is no statistically significance on a relative scale (ratio ORs p=0.21, ratio RRs p=0.27) while there is statistically significance on absolute scale (difference of RDs p=0.02).

Discussion

We found that almost all RCTs used relative effect measures to report subgroup analyses even when main effects where presented with an absolute effect measure. Most trials reported an OR or HR as measure of subgroup effect. This may be explained by the fact that most researchers are familiar with logistic regression or Cox proportional hazard regression from which subgroup effects can be derived by putting the interaction term in the model. Especially the frequent use of ORs as effect measure in RCTs is remarkable as the use of OR often lead to an overestimation of the effect as compared to RR.[14] There are several methods available to estimate subgroup effects with RR as measure of effect such as adding an interaction term in a log-binomial regression[15] or by calculating the ratio of RRs.[13]

Moreover, we demonstrated that results and conclusions changed with regard to statistical significance in one out of five trials when subgroup effects were calculated on a different scale than reported. Subgroups analyses which reveal statistical significant relative but non-statistical significant absolute effects, may have limited clinical relevance. For trials with non-statistical significant subgroup effects on a relative scale and statistical significant results on an absolute scale, we found both small and large absolute treatment effects among subgroups (Box 1 and Box 2).[11] [12] The clinical impact of such subgroup findings are, however, also highly dependent on (the severity of) the primary outcome of interest. This phenomenon is illustrated by the numerical example of Dondorp *et al.* (Box 1). Although the absolute effect size might be judged modest (difference of RDs: 4.5% (95% CI 0.9% to 8.1%), this finding may be clinically relevant due to the severity of the primary outcome, i.e. in-hospital mortality. This subgroup finding would not have been detected when results were only presented with relative subgroup effects. As a consequence, reporting of both relative and absolute subgroup effect measures is crucial for determining the clinical impact of subgroup results. Absolute subgroup effects (difference of RDs) can easily be derived by using Rothman's Episheet version June 11, 2008 (http://www.drugepi.info/links/down-loads/episheet.xls).

To our knowledge, this is the first study to investigate whether subgroups are reported as relative or absolute effect measures. Moreover, we studied the impact of such choices by calculating subgroup effects on a different scale than reported. To enhance validity, we performed a systematic literature search and included all RCTs that were published in five major general medical journals in 2010.
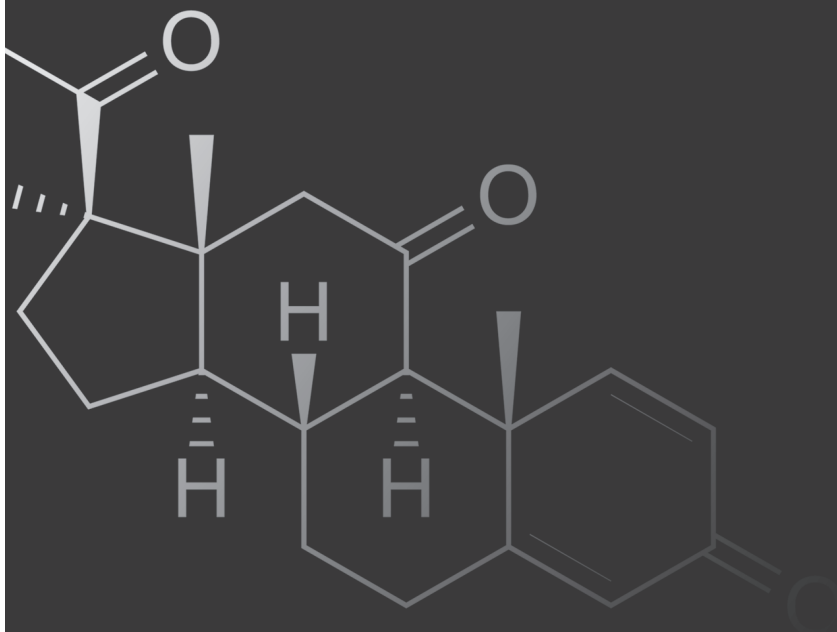
To appreciate our results, some potential limitations should also be discussed. Firstly, inclusion of RCTs in our study was restricted to trials that were published in 2010 in five major medical journals and our results may therefore not be generalisable to trials

published in less prominent journals. Secondly, we might have missed some RCTs with our PubMed search syntax. It is, however, unlikely that this would have affected our results since these RCTs are likely to be missing at random. Thirdly, we have included data from trials that reported HRs as effect measure for subgroup analysis, and which reported only events and absolute numbers of patients across subgroups (i.e. did not report person-time of follow-up across the subgroup). Results of these calculations cannot be directly linked to the results as presented in the articles. Our aim, however, was to investigate whether results would change if subgroup effects were calculated on both a relative and absolute scale. Since we were able to derive both relative (ratio of RRs) and absolute (difference of RDs) subgroup effects, we do not consider this as a drawback.   Finally, we pragmatically used a difference in statistical significance (p-value ≤ 0.05) to conclude whether relative and absolute subgroup effect differed. Although frequently used in medical science, the use of a p-value of ≤ 0.05 for statistical significance is arbitrary. Furthermore, not only statistical significance but also the magnitude of the reported effect size and the severity of the primary outcome of interest are of crucial importance when translating research findings into practice as illustrated by the numerical examples (Box 1 and Box 2).

In conclusion, almost all RCTs that are currently published in high impact journals use relative effect measures for reporting subgroup analyses. In 20% of the trials, conclusions changed when subgroup effects were calculated on a different scale than reported. Because of the potential for relative estimates to lead to misinterpretations of the absolute value of benefit, a strong argument could be made that the reporting of relative risk reduction should always be accompanied by presentation of absolute risk reductions. We therefore recommend to incorporate such recommendations in the CONSORT statement not only for primary and secondary outcomes but also for subgroup analyses.

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Chapter 6

General discussion

Optimising treatment of clinically diagnosed acute rhinosinusitis

Almost all patients with an episode of acute rhinosinusitis (ARS) are seen and treated in general practice. Although generally self-limiting within four weeks, ARS is accompanied by unpleasant symptoms and is frequently associated with impaired daily functioning. Numerous physicians and researchers all over the world have therefore tried to determine the optimal treatment strategy for ARS by performing more than 100 randomised controlled trials (RCTs). Most trials investigated the efficacy of antibiotics, but some also studied other treatments such as intranasal and systemic corticosteroids (in addition to antibiotics as well as monotherapy), non-steroidal anti-inflammatory drugs (NSAIDs), and nasal saline irrigation. Summarising all the existing evidence, we may conclude that none of the treatment options has convincingly proved to be beneficial in patients with clinically diagnosed ARS (Table 1). Patients with symptoms of ARS should therefore primarily be treated with symptomatic therapy, i.e. analgesics (paracetamol) and decongestive nosedrops (see Appendix: Flow diagram). Nevertheless, general practitioners (GPs) continue to prescribe antibiotics and intranasal corticosteroids (INCS) frequently in daily practice.[1] These suboptimal treatment strategies lead to high costs, undesirable side-effects and enhanced risk of reconsultations for similar complaints. Therefore, reduction of these unnecessary prescriptions is of major importance. Changing professional behavior in daily clinical practice is, however, known to be very difficult, especially when recommendations demand a change in existing routines and habits.[2] Providing an appropriate treatment alternative may be a potential solution. As findings of current trials are applicable to the broad population of patients with clinically diagnosed ARS representing a heterogeneous group of underlying aetiologies (such as viral, bacterial, allergic and idiopathic triggers causing paranasal mucosal infection, inflammation or dysregulation of the autonomic nervous system of the (sero)mucous glands)[3], potential beneficial effects in subgroups of patients might have been missed. Therefore, a strong recommendation can be made to continue the search for the most optimal treatment of patients with clinically diagnosed ARS. Future research efforts should focus on three main areas of interest: 1) identifying subgroups of patients with clinically diagnosed ARS that do benefit from antibiotics or corticosteroids; 2) determining the effectiveness of intranasal anticholinergics; 3) optimising current symptomatic treatment strategies, e.g. by studying the effectiveness of irrigation of the nose and adjacent sinuses.

Table 1. Summary of evidence table

Treatment	Acute rhinosinusitis confirmed by reference test	Clinically diagnosed acute rhinosinusitis
Antibiotics	Small benefit on clinical improvement (NNT=10) [4] Highly effective among patients with ARS as confirmed by CT (NNT=3) [5]	No beneficial effect even if symptoms sustain for 7-10 days [6]
Intranasal corticosteroids	Very modest beneficial effect on clinical improvement (NNT=15) [7]	No proven clinical beneficial effect of INCS monotherapy [8]
Systemic corticosteroids	Likely to have short-term clinical improvement when added to antibiotics (NNT=5) [9]	No clinical beneficial effect [10]
NSAIDs	No clinical beneficial effect as compared to systemic corticosteroids [11]	n/a
Decongestive therapy	No significant effects of peroral decongestants on the size of the sinus ostia when added to antibiotics [12]	n/a
Nasal irrigation with saline	n/a	No proven beneficial effect on clinical improvement [13]
Intranasal sodium cromoglycate	No beneficial effects on symptoms and radiological findings [14]	n/a
Steam inhalation	n/a	n/a
Intranasal anticholinergics	n/a	n/a
Antihistamines	No clinical improvement in children [15]	n/a

1. Identifying subgroups in ARS: searching for the needle in the haystack?

Current evidence on the use of antibiotics and corticosteroids reveals no beneficial effects of these agents in patients with symptoms of ARS. Are antibiotics and cortico-steroids therefore completely obsolete in patients with ARS? The answer to this question is probably no. The findings of current trials are applicable to the broad population of patients with clinically diagnosed ARS which represents a heterogeneous group of underlying aetiologies. As a consequence, potential beneficial effects in subgroups of patients may have been missed. Future research efforts should therefore focus on identifying subgroups of patients that do benefit from antibiotics or cortico-steroids. The proof of principle are recent studies on a similar phenomenon in medicine, i.e. acute otitis media, in which subgroups have been identified that do benefit from antibiotics.[16] [17] Knowing this, the question arises whether we are also able to identify such subgroups in clinically diagnosed ARS. Until now, we have not been able to distinguish between patients that benefit more and those that do not benefit at all from specific treatments. Below, we further explore patient characteristics and diagnostic tools that might contribute to detecting such subgroups among the broad population of patients with clinically diagnosed ARS.

Patient characteristics and near-patients tests to predict beneficial effects of antibiotics

In a RCT of Lindbaek *et al*. among patients with ARS as confirmed by the presence of air-fluid level or total opacification on computed tomography (CT) scanning, antibiotics appeared to be highly effective (number needed to treat = 3).[5] Although no subsequent trial with CT scanning has been performed to reproduce the reported effects, the results suggest that there indeed might be a subgroup among the broad population of patients with clinically diagnosed ARS that would benefit from antibiotics. This phenomenon has been recognised by Young *et al*. which performed a meta-analysis of individual patient data of ten RCTs on the effectiveness of antibiotics in patients with clinically diagnosed ARS in order to identify such subgroups.[6] Unfortunately, no predictors could be detected among common clinical signs and symptoms. Main criticism to this meta-analysis is the fact that the pooled population of individual patients were still too heterogeneous (and thus not discriminative enough to predict beneficial effects of antibiotics) due to the broad inclusion criteria used in all included trials.[18] Moreover, this meta-analysis of individual patient data did not investigate whether specific patient characteristics such as presence or absence of underlying allergic and non-allergic rhinitis, or point-of-care test results are of predictive value for beneficial effects of antibiotics.

Despite these criticisms, we still can conclude that identification of subgroups of patients that would benefit from antibiotics is far from easy. It has been suggested that future studies should focus on deriving a diagnostic model of patient characteristics, clinical signs, symptoms and additional point-of-care tests which can accurately discriminate between a positive and negative CT scan in patients with clinically diagnosed ARS in order to detect subgroups that would benefit from antibiotics.[19 20] Such a diagnostic study however requires large number of patients, research funding and personnel. Moreover, if any simple and feasible prediction model could be derived in the near future, additional trials on the effectiveness of antibiotics are needed to validate such a model before applying its results into clinical practice.

Patient characteristics to predict beneficial effects of corticosteroids

Post-hoc subgroup analyses of our RCT revealed a strong trend towards a beneficial effect of systemic corticosteroids among the subgroup of patients with symptoms of rhinitis (not related to the flu or a cold) for at least 3 months per year.[10] Such post-hoc subgroup finding should always be interpreted with caution. Nevertheless, this finding may be relevant for clinical practice as it is supported by the available evidence on the effectiveness of corticosteroids for chronic rhinosinusitis.[21 22] Furthermore, since we excluded patients in our trial that used INCS in the previous four weeks, our results are not applicable to these patients. It is, however, likely that patients have a valid reason for using INCS, such as (non)allergic rhinitis. Based on the efficacy of corticosteroids in

(non)allergic rhinitis[23] [24], systemic corticosteroids may also have beneficial effects in these patients when suffering from ARS. Future studies on the effectiveness of (intranasal) corticosteroids in patients with clinically diagnosed ARS should therefore focus on subgroups of patients that suffer from underlying symptoms of chronic nasal symptoms and/or (non)allergic rhinitis.

Diagnostic tool that discriminates between viral and bacterial sinus infection

In the ideal world, the GP would have access to a simple, near-patient test that is able to accurately discriminate between patients with ARS who suffer from symptoms of a viral origin and those who suffer from a bacterial sinus infection. Unfortunately, nowadays no such diagnostic test is available. Diagnostic accuracy of tests such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) is too low to be implemented in daily practice.[25] [26] Future research into new diagnostic tests should focus on determining the amount of leukocytes and bacteria in sinonasal mucus. Studies on microscopic sputum examination revealed that the presence of both leucocytes (≥ 25 per microscopic field) and bacteria (≥ 10 per microscopic field) are suggestive for a bacterial infection of the lower respiratory tract.[27] [28] High microscopic bacterial and leukocyte counts in sinonasal mucus might therefore be predictive for a bacterial sinus infection in which antibiotics may have beneficial effects.

Diagnostic tool that detects the presence or absence of inflammation in sinonasal mucus

Chronic inflammation of the airway mucosa in patients with asthma or chronic obstructive pulmonary disease (COPD) is accompanied by abnormal local secretion of proteins and plasma proteins leakage.[29-31] Additionally, a previous study revealed that high levels of plasma proteins in sputum of patients with asthma was correlated to bronchial hyperreactivity[32] and other studies demonstrated that treatment with corticosteroids lead to reduced protein leakage into sputum.[33] [34] As a consequence, high protein levels in sinonasal mucus of patients with ARS may be correlated to an inflammatory process of the paranasal mucosa with similar characteristics of bronchial inflammation in patients with asthma. Therefore, future studies should be initiated to determine whether rapid tests can be developed that are able to accurately determine the level of albumin in (sino)nasal mucus, and whether such measurements are associated with the presence or absence of a major inflammatory component. High albumin levels in (sino)nasal mucus might in turn be predictive for beneficial effects of corticosteroids in patients with clinically diagnosed ARS.

2. Paradigm shift: pivotal role of autonomic nervous system dysregulation?

The primary objective of this thesis was to determine whether anti-inflammatory treatment could provide symptom resolution in the broad population of patients with clinically diagnosed ARS. We demonstrated that (systemic) corticosteroids are not effective for treating these symptoms. This conclusion leads to additional hypotheses regarding the causation of the clinical signs and symptoms of patients with ARS. It could be possible that symptoms such as nasal congestion and nasal discharge occur due to dysregulation of the autonomic nervous system of the (sero)mucous glands. Consequently, inhibition of this hypersecretion of nasal (sero)mucous glands by anticholinergics could provide symptom relievement. A recent Cochrane review on the use of intranasal ipratropium bromide in patients with a common cold reported that intranasal anticholinergics are likely to have a beneficial effect on rhinorrhea.[35] However, no effects on nasal congestion was observed. Future studies are necessary to determine the effectiveness of intranasal ipratropium bromide in patients with clinically diagnosed ARS without underlying (non)allergic and chronic nasal symptoms.

3. Improving symptomatic treatment, e.g by studying the effectiveness of irrigation of the nose and adjacent sinuses

Current symptomatic treatment options are limited to the use of intranasal decongestants, steam inhalation therapy, and nasal irrigation with saline as added to analgesics (i.e. paracetamol). These treatments have no proven beneficial effects in patients with ARS (Table 1). Suboptimal symptomatic treatment may subsequently result in unnecessary antibiotic or intranasal corticosteroid prescriptions. To increase patients' self-management and reduce patients' inclination to consult a GP for these complaints, optimising symptomatic treatment is warranted. In the United States and the United Kingdom, there is a growing tendency to wash the nasal cavity of patients with symptoms of rhinosinusitis with a sinus irrigation device (for instance a so-called neti pot) in order to flush out excess mucus from the nose and the sinuses. A Cochrane review on the use of nasal saline irrigation for chronic rhinosinusitis revealed a beneficial effect of such treatment.[36] Future studies are needed to determine the effectiveness of nasal irrigation with a sinus irrigation device in patients with symptoms of ARS.

Current practice

Currently, no treatment has convincingly proved its beneficial effects in the broad population of patients with clinically diagnosed ARS. Clinical guidelines have adopted these considerations and recommend to restrict the use of antibiotics and (intranasal) corticosteroids in this condition.[37] [38] Withdrawing from these treatments does, however, not mean that GPs are condemned to a wait and see policy. Main reasons for consultation are patients' inconvenient symptoms such as nasal congestion, nasal discharge and facial pain. Relieving symptoms should therefore be initiated by prescribing decongestive nosedrops and analgesics (e.g. paracetamol). An appropriate symptomatic treatment regimen should comprise high dosages paracetamol (i.e. 1000 mg three daily), and should be continued until complete resolution of symptoms has been achieved.

However, implementation of such symptomatic treatment approach into daily practice remains challenging given the high antibiotic and INCS prescription rates.[1] Over time, numerous studies have been performed to determine the efficacy of specific interventions to reduce unnecessary antibiotic prescriptions for (upper) respiratory tract infections in general practice. Nevertheless, it is unknown which combination of interventions lead to the highest and most sustainable reduction in daily practice.[39] Effectiveness of such interventions are likely to differ between countries due to country-specific organisation of health care. For example, a large scale information campaign aimed at educating both physicians and parents has demonstrated to reduce the amount of antibiotic prescriptions for children in the United States.[40] It is, however, questionable whether the costs of such campaigns would outweigh the benefits in the Netherlands as antibiotic prescription rates are relatively low as compared to other countries.[41]

Future practice: "shared expectations"

In the Netherlands, the largest reduction of unnecessary prescriptions may be achieved by improving GPs' communication skills. GPs' overestimation of patients' expectations towards antibiotic prescriptions is known to be an important cause of unnecessary antibiotic prescriptions in daily practice. This mismatch can be solved by applying a "shared-decision making" model into daily practice.[42] [43] Important elements of this model are the fact that patients' expectations should be explored explicitly and that potential treatment options should be explained including the evidence regarding their benefits and harms. Explicit exploration of expectations during consultation may lead to "shared expectations" which in turn may lead to a reduction of unnecessary prescriptions. Moreover, it is unlikely that such an approach would affect patient satisfaction as previous studies revealed that providing medical information about

patients' symptoms and its natural course are equally important for patients as prescribing antibiotics.[44] [45] Recent studies confirmed that improving GPs' communication skills do result in a reduction of antibiotic prescriptions for respiratory tract infections.[46-48]
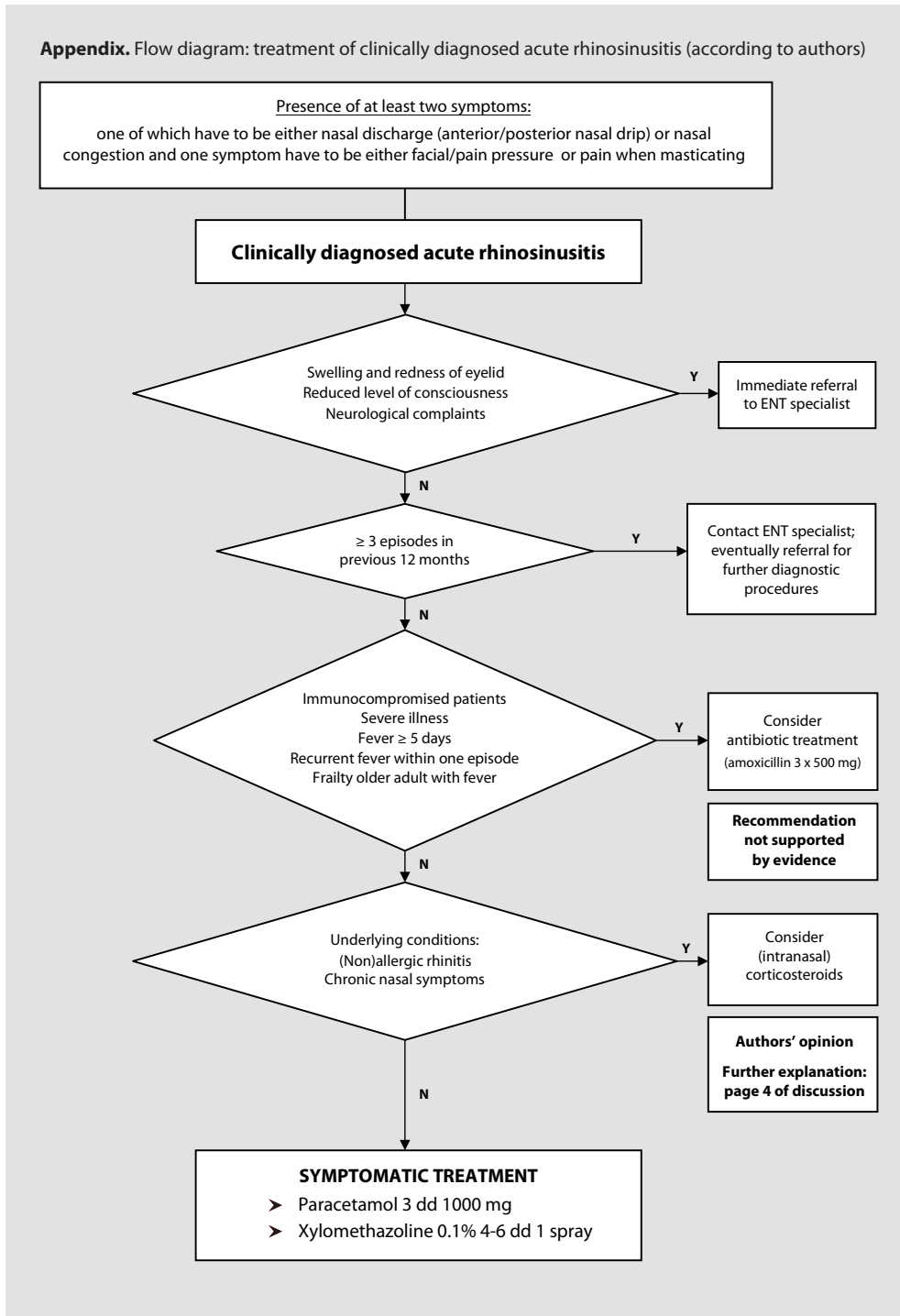
Conclusion

In summary, nowadays no beneficial treatment is available for clinically diagnosed ARS.

Future studies should focus on:

- Identifying subgroups of patients that do benefit from antibiotics or corticosteroids; future research projects need to investigate the use of specific patient characteristics and/or diagnostic tools which are able to detect the presence of a bacterial infection or specific inflammation based on sinonasal mucus examination.

- Determining the effectiveness of intranasal anticholinergics in patients without underlying chronic nasal symptoms and (non)allergic rhinitis.

- Optimising symptomatic treatment, for example by studying the effectiveness of irrigation of the nose and adjacent sinuses

Until an effective treatment strategy has been identified, the treatment of patients with clinically diagnosed ARS should be based on symptomatic treatment (adequate and regular use of decongestive nose drops and high doses of analgesics).

Appendix. Flow diagram: treatment of clinically diagnosed acute rhinosinusitis (according to authors)

> Presence of at least two symptoms:
> one of which have to be either nasal discharge (anterior/posterior nasal drip) or nasal congestion and one symptom have to be either facial/pain pressure or pain when masticating

Clinically diagnosed acute rhinosinusitis

Swelling and redness of eyelid
Reduced level of consciousness
Neurological complaints

— Y → Immediate referral to ENT specialist

N

≥ 3 episodes in previous 12 months

— Y → Contact ENT specialist; eventually referral for further diagnostic procedures

N

Immunocompromised patients
Severe illness
Fever ≥ 5 days
Recurrent fever within one episode
Frailty older adult with fever

— Y → Consider antibiotic treatment
(amoxicillin 3 x 500 mg)

Recommendation not supported by evidence

N

Underlying conditions:
(Non)allergic rhinitis
Chronic nasal symptoms

— Y → Consider (intranasal) corticosteroids

Authors' opinion

Further explanation: page 4 of discussion

N

SYMPTOMATIC TREATMENT
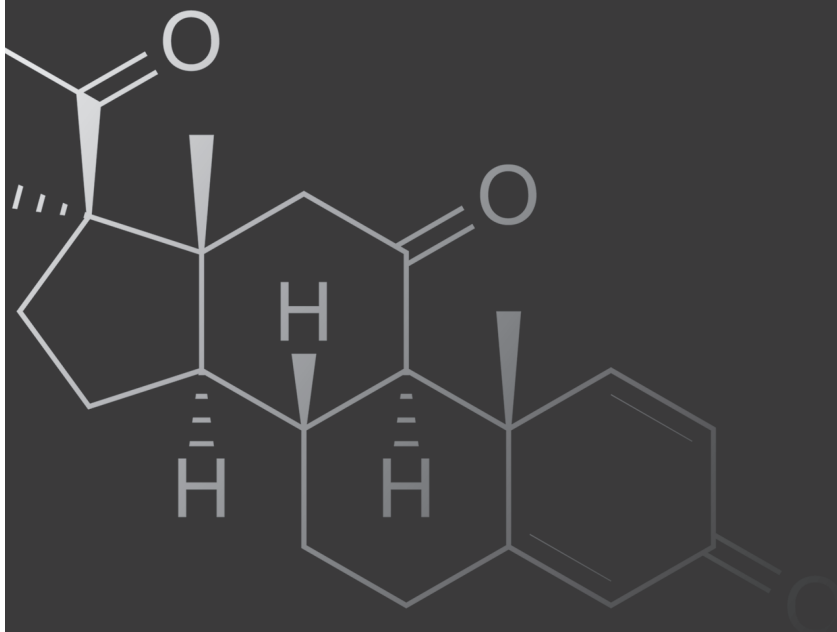➤ Paracetamol 3 dd 1000 mg
➤ Xylomethazoline 0.1% 4-6 dd 1 spray

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Chapter 7

Summary

Samenvatting

Dankwoord

Curriculum Vitae

Chapter 7

Summary

Samenvatting

Dankwoord

Curriculum Vitae

Traditionally, acute rhinosinusitis (ARS) has been regarded as a bacterial infection of the paranasal sinuses. Therefore, numerous randomised controlled trials (RCTs) have been performed to determine the clinical effectiveness of oral antibiotics in patients with ARS. Summarising the results of these studies, we can conclude that antibiotics should not be advocated even if symptoms persist for ten days. Nowadays, acute inflammation of the paranasal mucosa due to infectious (e.g. viruses, bacteria) and non-infectious (allergens, idiopathic triggers) causes is increasingly considered as the predominant path in the causation of symptoms in ARS. Based on this pathophysiological consideration, anti-inflammatory drugs might be effective by attenuating the host inflammatory response. As a consequence, (intranasal) corticosteroids could be a treatment option in clinically diagnosed ARS. Current evidence on their benefits is, however, inconclusive. In this thesis, we aimed to evaluate the effectiveness of corticosteroids in clinically diagnosed ARS.

In **chapter 2,** a retrospective cohort study within the computerised database of the Utrecht General Practitioners Research Network is reported. The aim of this study was to provide information on general practitioners' prescribing and referral patterns before and after the introduction of a revised guideline on ARS in 2005. This revised guideline advocates a more judicious use of antibiotics in patients with symptoms of ARS in general practice, and to limit the use of intranasal corticosteroids (INCS) to patients in which previous treatment options have failed. Clinical diagnoses of ARS were recorded according to ICPC codes (R75 and/or R09) and drug prescriptions according to ATC codes. Over time, ARS incidence rates did show a stable pattern, with an average incidence rate of approximately 29 episodes per 1000 person-years. From 2000 to 2005, the overall antibiotic prescription rate increased from 56 to 62 prescriptions per 100 episodes. From 2005 onwards, the overall antibiotic prescription decreased to 56 per 100 episodes in 2009 (p-value for difference in trend over time < 0.05). After the introduction of the guideline in 2005, the overall INCS prescription rate increased from 20 per 100 episodes in 2005 to 31 per 100 episodes in 2009 (RD: 11; 95% CI: 7 to 15, p-value for difference in trend over time < 0.01). We concluded that despite strong recommendations of the revised ARS guideline to restrict the use of antibiotics and INCS, only a modest decrease in antibiotic prescription rates over recent year was observed, whereas INCS prescription rates even increased.

In **chapter 3** two systematic reviews of the literature on the effects of cortico-steroids in ARS are presented. **Chapter 3.1** describes a systematic search in the electronic medical databases to determine the efficacy of INCS as a monotherapy in ARS. The search yielded 490 papers of which only two were relevant and had a high validity regarding for

answering our research question. One factorial designed RCT, did neither report a difference in the proportion of clinically cured patients at day 10 (aRD: 0% (95% CI: -12.6% to 12.7%)) nor in the total symptom score at day 10. Another large RCT reported a statistically significant difference in mean Major Symptom Score (MSS) over the 15-day treatment period within both INCS groups (once and twice daily) as compared to the placebo group. However, the clinical relevance of mean MSS as primary endpoint is debatable and the size of the reported effect in this study is modest. We therefore concluded that the clinical beneficial effect of INCS as a monotherapy has not been established in patients with ARS.

In **chapter 3.2** the effectiveness of systemic corticosteroids in relieving symptoms of ARS is assessed by performing a systematic review and meta-analysis. A total of 2630 records were retrieved from the initial search. Removing duplicates left 1710 original articles. Four RCTs with a total of 1008 adult participants were included. These studies were judged to be of moderate methodological quality. ARS was defined clinically in all trials. However, the three trials performed in ENT outpatient clinics also used radiological assessment as part of their inclusion criteria. All participants received oral antibiotics and were assigned to either oral corticosteroids (prednisone 24-80 mg daily or betamethasone 1 mg daily) or the control treatment (placebo in three trials and non-steroidal anti-inflammatory drugs (NSAIDs) in one trial). In all trials, participants treated with oral corticosteroids were more likely to have short-term resolution or improvement of symptoms than those receiving the control treatment: at days 3 to 7, risk ratio (RR) 1.4, 95% CI 1.1 to 1.8; risk difference (RD) 20% (6% to 34%) and at days 4 to 10 or 12, RR 1.3, 95% CI (1.0 to 1.7), RD 18% (3% to 33%). An analysis of the three trials with placebo as a control treatment demonstrated similar results but with a lesser effect size. Scenario analysis revealed that outcomes missing from the trial reports might have introduced selection bias. Reported side-effects of oral corticosteroids were limited and mild. We concluded that oral corticosteroids are likely to be effective in short-term relief of symptoms in ARS as an adjunctive therapy to oral antibiotics. However, current evidence is limited and has a significant risk of bias. Therefore, additional high-quality trials assessing the efficacy of systemic corticosteroids both as an adjuvant and as a monotherapy should be initiated to provide a more definite answer on their benefits in patients with ARS.

Chapter 4 describes the results of a double blind, placebo-controlled, randomised clinical trial to assess the effectiveness of systemic corticosteroids (prednisolone 30 mg daily for seven days) in adult patients who visited their general practitioner (GP) with signs and symptoms of ARS for at least five days. A total of 68 GPs out of 54 general practices in the province Zeeland, recruited 185 patients aged 18 years and older with clinically diagnosed ARS (defined as ≥ 2 diagnostic criteria: nasal discharge or nasal congestion and facial pain/pressure or pain when masti-cating). The primary outcome was the proportion of patients with resolution of

facial pain/pressure at day 7. Secondary outcomes were time to resolution of symptoms, median duration of symptoms, and health related quality of life (HRQoL). A total of 185 patients (prednisolone n=93; placebo n=92) were randomised. Two participants withdrew from study and nine participants were excluded from primary analysis because of incomplete symptom reporting, leaving 174 (n=88; n=86) patients for intention-to-treat analysis. The proportions of patients with resolution of facial pain/pressure at day 7 were 55 out of 88 (62.5%) in the prednisolone group versus 48 out of 86 (55.8%) in the placebo group (RD 6.7%, 95% CI -7.9% to 21.2%). The proportion of patients with decreased symptoms was similar in both groups. HRQoL did not differ between those in the prednisolone and those in the placebo group across the different time points. Although no statistical significant interaction effect was found in sub-group analyses, post-hoc subgroup analysis of patients with chronic nasal symptoms revealed a strong trend towards beneficial effects of corticosteroids. Adverse events reported were mild and did not differ between the groups. We concluded that systemic corticosteroids have no clinically relevant beneficial effects in the broad population of patients with clinically diagnosed ARS.

Chapter 5 addresses whether relative (e.g. relative risk (RR), odds ratio (OR), hazard ratio (HR)) or absolute (e.g. risk difference (RD)) effect measures were used in subgroup analyses of RCTs, and whether these subgroup effect measures differed from the main effect measures. We also studied whether conclusions would change if subgroup effects were calculated on a different scale than reported. All RCTs (n=327) published in 2010 in five major general medical journals (AIM, BMJ, JAMA, Lancet and NEJM) were studied. For trials with a dichotomous primary outcome, the effect measures for both the main and subgroup effects were extracted. If crude data of subgroups were reported, subgroup effects on both a relative and an absolute scale were calculated. Of the 229 RCTs with a dichotomous primary outcome, 120 (52%) performed subgroup analyses. In 106 of these 120 RCTs (88%), relative effect measures were used for subgroup analyses, whereas subgroup effects were presented on an absolute scale in nine trials (8%). Two RCTs (2%) reported both relative and absolute subgroup effects. Most of the 120 trials (74%) reported the same effect measure for the main and subgroup effect. However, eight trials (7%) that used an absolute effect measure for the main effect (RD) assessed subgroup effects on a relative scale (OR, HR). We were able to extract crude data of subgroups in 61 of the 120 RCTs (51%). Calculating subgroup effects on a different scale then reported lead to a change in conclusion in one out of five trials. We concluded that almost all RCTs used relative effect measures for subgroup analyses. Moreover, interpretation of subgroup effects appeared to be dependent on whether relative or absolute effect measures were used. Reporting of relative risk reduction should therefore always be accompanied by presenting the absolute risk reduction.

In **chapter 6** we discuss the treatment options for ARS in a broader perspective and provide recommendations for both clinical practice and future research.

Summarising all the available evidence, we may conclude that no treatment regimen has convincingly proved to shorten the duration of illness of clinically diagnosed ARS. Patients with symptoms of ARS should therefore primarily be treated with symptomatic therapy, i.e. analgesics (paracetamol) and decongestive nosedrops. Nevertheless, antibiotics and INCS are still frequently prescribed in daily practice. Changing such professional behavior is known to be very difficult, especially when these demand a change in existing routines and habits. Providing an appropriate treatment alternative may be a potential solution. Future research should therefore focus on three main areas of interest: 1) identifying subgroups of patients with clinically diagnosed ARS that do benefit from antibiotics or corticosteroids, 2) determining the effectiveness of anticholinergics, and 3) optimising current symptomatic treatment strategy

1) Current trial findings are applicable to the broad population of patients with clinically diagnosed ARS representing a heterogeneous group of underlying aetiologies. Potential benefits of interventions in subgroups of patients may therefore have been missed in the existing RCTs. The proof of principle are recent studies on a similar phenomenon in medicine, i.e. acute otitis media, in which subgroups have been identified that do benefit from antibiotics. Future research projects need to investigate the use of specific patient characteristics and near patient test that are able to accurately predict beneficial effects of specific treatments and/or diagnostic tools which are able to detect the presence of a bacterial infection or inflammation based on sinonasal mucus examination.

2) The findings presented in this thesis reveal that corticosteroids are not effective for treating the broad population of patients with clinically diagnosed ARS. This conclusion leads in turn to additional hypotheses regarding the causation of the clinical signs and symptoms. It could be possible that symptoms such as nasal congestion and nasal discharge occur due to dysregulation of the autonomic nervous system of the (sero)mucous glands. Consequently, inhibition of this hypersecretion of nasal (sero)mucous glands by anticholinergics could provide symptom relievement. Additional trials should, therefore, determine the effectiveness of intranasal anticholinergics in patients without underlying chronic nasal symptoms and/or (non)allergic rhinitis.

3) Current symptomatic treatment options have no proven beneficial effects in patients with ARS. Suboptimal symptomatic treatment may in turn lead to unnecessary antibiotic or INCS prescriptions. To increase patient self-support and reduce patients' inclination to consult a GP for these complaints, optimising symptomatic treatment is warranted. In the United States and the United Kingdom, there is a growing tendency to wash the nasal cavity of patients with sinonasal complaints with a sinus irrigation device (for instance a so-called neti pot) in order to flush out excess mucus from the nose and the sinuses. A Cochrane review on the use of nasal saline irrigation for chronic rhinosinusitis revealed beneficial effects of such treatment. Future studies are needed to determine the efficacy of nasal irrigation with a sinus irrigation device in patients with symptoms of ARS.

In summary, nowadays no beneficial treatment is available for clinically diagnosed ARS. Until an effective treatment strategy has been identified, the treatment should be based on symptomatic therapy (decongestive nose drops and high doses analgesics). However, implementation of such symptomatic treatment approach into daily practice remains challenging given the high antibiotic and INCS prescription rates. In the Netherlands, improving GPs' communication skills is likely to be the most effective way to achieve a change in this professional prescribing behavior. Therefore, a strong argument must be made to apply a "shared decision making" model into daily practice. In this model GPs should explicitly explore patients' expectations and explain potential treatment options including the evidence regarding their benefits and harms.

Chapter 7

Van oudsher wordt acute rhinosinusitis (ARS) beschouwd als een bacteriële infectie van de paranasale sinussen. Zodoende zijn talrijke gerandomiseerde gecontroleerde trials (RCTs) verricht om de klinische effectiviteit van orale antibiotica bij patiënten met ARS te bepalen. Op basis van de resultaten van deze studies kan geconcludeerd worden dat antibiotica niet routinematig dient te worden voorgeschreven, zelfs niet als de klachten langer dan tien dagen bestaan. Een meer recente hypothese veronderstelt dat acute inflammatie van de paranasale slijmvliezen als gevolg van infectieuze (bijvoorbeeld virussen, bacteriën) en niet-infectieuze (bijvoorbeeld allergenen, idiopathische triggers) oorzaken een vooraanstaande rol spelen bij het ontstaan van ARS. Als deze hypothese klopt dan zouden anti-inflammatoire middelen effectief kunnen zijn. Het huidige bewijs met betrekking tot de effectiviteit van deze middelen is echter niet eenduidig. Ons doel was daarom om de effectiviteit van corticosteroïden bij patiënten met klinisch gediagnosticeerde ARS te evalueren.

In **hoofdstuk 2** beschrijven we de resultaten van een cohort studie, waarin we het voorschrijf- en verwijsgedrag voor en na de introductie van een gereviseerde ARS richtlijn in 2005 bestudeerden. De gereviseerde richtlijn adviseert een meer rationeel gebruik van antibiotica bij patiënten met klachten van ARS in de huisartspraktijk, terwijl intranasale corticosteroïden (INCS) alleen overwogen kunnen worden bij patiënten bij wie eerdere behandelopties geen succes hadden. De klinische diagnose ARS was gebaseerd op de ICPC coderingen (R75 en/of R09); medicatie werd volgens de ATC coderingen gerapporteerd. De gemiddelde incidentie van ARS was min of meer constant met 29 episoden per 1000 persoonsjaren. Van 2000 tot 2005 nam het aantal antibiotica voorschriften toe van 56 naar 62 voorschriften per 100 episoden. Vanaf 2005 daalde het aantal antibiotica voorschriften naar 56 per 100 episoden in 2009 (p-waarde trend: < 0.05). Na de introductie van de richtlijn in 2005 nam het aantal voorgeschreven INCS preparaten toe van 20 per 100 episoden in 2005 naar 31 per 100 episoden in 2009 (RD: 11, 95% CI: 7 to 15, p-waarde trend: < 0.01). Ondanks de duidelijke aanbevelingen in de gereviseerde ARS richtlijn om het gebruik van antibiotica en INCS te beperken, vonden we dus slechts een kleine daling in het aantal voorgeschreven antibioticakuren, terwijl het aantal voorgeschreven INCS preparaten zelfs toenam.

In **hoofdstuk 3** beschrijven we de resultaten van twee systematische literatuurstudies naar de effecten van corticosteroïden bij patiënten met ARS. **Hoofdstuk 3.1** geeft een overzicht van het beschikbare bewijs van het effect van INCS als monotherapie bij ARS. De systematisch uitgevoerde zoekactie in elektronische medische databases leverde 490 artikelen op, waarvan er slechts twee relevant en valide waren. Een RCT met een factoriële onderzoeksopzet (dat wil zeggen dat er in één studie twee behandelingen gelijktijdig

worden onderzocht (in deze studie betrof het een antibioticum en INCS) waardoor er in totaal vier behandelgroepen worden gevormd) liet geen verschil in herstel zien op dag 10 tussen de groep patiënten die behandeld werden met INCS en de groep die een placebo ontvingen (aRD: 0% (95% CI: -12.6% to 12.7%)). Ook de totale symptoom score op dag 10 verschilde niet tussen beide groepen. Een andere grote RCT liet juist wel een statistisch significant verschil in symptoom score zien tussen de INCS groepen (één- en tweemaal daags) en de placebo groep. Het effect was echter klein en men kan zich afvragen hoe relevant een gemiddelde symptoom score is voor de dagelijkse praktijk. We concludeerden dan ook dat een klinisch relevant effect van INCS als monotherapie bij patiënten met ARS nog niet bewezen is.

De systematische literatuurstudie in **hoofdstuk 3.2** beschrijft het bewijs met be-trekking tot de effectiviteit (verminderen van symptomen) van systemische cortico-steroïden bij patiënten met ARS. De initiële zoekactie leverde 1710 originele artikelen op. Vier RCTs met in totaal 1008 patiënten en een matige methodologische kwaliteit werden geïncludeerd. Alle vier de artikelen hanteerden een klinische definitie van ARS, waarbij drie van de vier studies ook radiologisch onderzoek als onderdeel van hun inclusiecriterium hanteerden. Alle deelnemers ontvingen orale antibiotica en werden gerandomiseerd over twee groepen, te weten een orale corticosteroïden groep (prednison 24-80 mg per dag of betamethason 1 mg per dag) en een controle groep (placebo in drie onderzoeken en NSAIDs in een onderzoek). Deelnemers die behandeld werden met orale corticosteroïden hadden meer kans op resolutie of ver-betering van klachten op korte termijn dan de deelnemers in de controle groep: dag 3-7, relatief risico (RR) 1.4, 95% CI 1.1 tot 1.8; absoluut risicoverschil (RD) 20% (6% tot 34%) en op dag 4-10 or 12, RR 1.3, 95% CI (1.0 tot 1.7), RD 18% (3% tot 33%). Een analyse van de drie onderzoeken met een placebo-gecontroleerde onderzoeks-arm toonde vergelijkbare resultaten, maar het effect was minder groot. Selectie bias ten gevolge van missende waarden voor de uitkomsten kan echter niet worden uitgesloten. De gerapporteerde bijwerkingen van orale corticosteroïden bleken gering en mild. Op basis van deze literatuurstudie lijken orale corticosteroïden tezamen met antibiotica effectief te zijn voor wat betreft het verlichten van de klachten op korte termijn bij patiënten met ARS. Het beschikbare bewijs is echter beperkt en kan vertekend zijn ten gevolge van de matige methodologische kwaliteit alsmede het grote aantal missende waarden voor de uitkomst. Het is dan ook noodzakelijk dat er nieuwe onderzoeken met een goede methodologische kwaliteit worden verricht om de effectiviteit van systemische corticosteroïden zowel als adjuvante en als monotherapie bij patiënten met klachten van ARS te kunnen bepalen.

In **hoofdstuk 4** beschrijven we de resultaten van een dubbel blinde, placebo-gecontroleerde, gerandomiseerde klinische studie naar het effect van systemische corticosteroïden (prednisolon 30 mg gedurende zeven dagen) bij patiënten die hun huisarts bezochten met klachten van ARS. In totaal rekruteerden 68 huisartsen van 54 huisartspraktijken in Zeeland 185 volwassen patiënten met klinische gediagnosticeerde ARS (gedefinieerd als ≥ 2 diagnostische criteria: nasale afscheiding of verstopte neus en pijn/druk in het aangezicht of pijn bij kauwen). De primaire uitkomst was de proportie van patiënten met resolutie van pijn/druk in het aangezicht op dag 7. Secundaire uitkomsten waren: snelheid van herstel, mediane duur van klachten, en ziekte-specifieke kwaliteit van leven (KvL). In totaal werden er 185 deelnemers gerandomiseerd (prednisolon n=93; placebo n=92). Twee deelnemers trokken zich terug van de studie en negen deel-nemers werden geëxcludeerd voor de primaire analyse vanwege incomplete rapportage van symptomen, waardoor er 174 patiënten (n=88; n=86) overbleven voor de intention-to-treat analyse. Op dag 7 hadden 55 van de 88 (62.5%) in de prednisolon groep en 48 van de 86 (55.8%) in de placebo groep geen pijn/druk in het aangezicht meer (RD 6.7%, 95% CI -7.9% to 21.2%). Ook het aantal patiënten met verminderde klachten en de kwaliteit van leven was gelijk in beide groepen. Patiënten met chronische neusklachten leken meer baat te hebben bij corticosteroïden, maar het effect was niet statistisch significant en het gevonden effect werd min of meer door toeval ontdekt. De gerapporteerde bijwerkingen waren mild en verschilden niet tussen de groepen. Op basis van de resultaten concluderen we dat systemische corticosteroïden geen klinisch relevant effect hebben bij patiënten met klinisch gediagnosticeerde ARS.

In **hoofdstuk 5** beschrijven we de resultaten van een methodologische studie waarin we gekeken hebben of onderzoekers relatieve (bijvoorbeeld relatief risico (RR), odds ratio (OR), hazard ratio (HR)) dan wel absolute (bijvoorbeeld absoluut risicoverschil (RD)) effect-maten gebruiken om subgroepanalysen te rapporteren. Bovendien hebben we gekeken of de gebruikte effectmaten voor subgroepanalysen verschillen van de uitkomstmaten van de hoofdeffecten. Daarnaast bestudeerden we of conclusies zouden veranderen als de subgroepeffecten werden berekend op een andere schaal dan gerapporteerd. Hier-toe bestudeerden we alle RCTs (n=327) die in 2010 in vijf grote algemene medische tijd-schriften (AIM, BMJ, JAMA, Lancet and NEJM) werden gepubliceerd. Van de 229 RCTs met een dichotome primaire uitkomst, verrichtten er 120 (52%) subgroepanalysen. Bij 106 van deze 120 RCTs (88%) werden relatieve effectmaten voor subgroepanalysen gebruikt, terwijl negen onderzoeken (8%) subgroepeffecten op een absolute schaal rapporteerden. Twee RCTs (2%) rapporteerden zowel relatieve als absolute subgroep-effecten. De meeste van de 120 onderzoeken (74%) rapporteerden dezelfde effectmaat voor zowel het primaire als het subgroepeffect. Echter, acht onderzoeken (7%) die een

absolute effect maat (RD) voor het primaire effect gebruikten rapporteerden de subgroep-effecten op een relatieve schaal (OR, HR). Bij 61 van de 120 RCTs (51%) konden we ruwe data voor subgroepen extraheren. Het berekenen van subgroepeffecten op een andere schaal dan gerapporteerd, leidde bij een op de vijf onderzoeken tot een andere conclusie. De meeste RCTs blijken een relatieve effectmaat te gebruiken voor subgroepanalysen, maar de interpretatie van subgroepeffecten is afhankelijk van de gebruikte effectmaten werden gebruikt. Wij adviseren daarom om ook bij subgroepanalysen zowel de relatieve risico reductie als de absolute risico reductie te rapporteren.

In **hoofdstuk 6** worden de diverse behandelopties voor ARS in een breder perspectief geplaatst en geven we enkele aanbevelingen voor zowel de dagelijkse praktijk als voor vervolgonderzoek.

Al het wetenschappelijke bewijs samenvattend, kunnen we concluderen dat geen enkele behandeling de duur van de klachten bij klinisch gediagnosticeerde ARS overtuigend verkort. Patiënten met symptomen van ARS dienen daarom primair symptomatisch te worden behandeld, dat wil zeggen met pijnmedicatie (paracetamol) en decongestieve neusdruppels. Toch worden antibiotica en INCS in de dagelijkse praktijk frequent voorgeschreven bij patiënten met ARS. Het doorbreken van dit voorschrijfgedrag is erg moeilijk, aangezien dit gepaard dient te gaan met een verandering in de bestaande routines en gewoonten. Een mogelijke oplossing voor dit probleem zou het aanreiken van geschikte, alternatieve behandelmogelijkheden kunnen zijn. Toekomstig onderzoek dient zich daarom te richten op drie belangrijke punten: 1) het identificeren van sub-groepen van patiënten met klinische gediagnosticeerde ARS die voordeel hebben van antibiotica of corticosteroïden, 2) het vaststellen van de effectiviteit van anticholinergica, en 3) het optimaliseren van de huidige symptomatische behandeling.

1) De bevindingen van de huidige onderzoeken zijn van toepassing op de algemene populatie van patiënten met klinisch gediagnosticeerde ARS. Deze patiënten vertegenwoordigen samen een heterogene groep van onderliggende oorzaken. Eventuele gunstige effecten van interventies kunnen derhalve gemist zijn in bepaalde subgroepen. Een mooi voorbeeld hiervan is een soortgelijke klacht in de huisartspraktijk, namelijk otitis media acuta. Bij dit ziektebeeld zijn subgroepen ontdekt die voordeel hebben bij antibiotica. Toekomstige onderzoeksprojecten dienen het gebruik van specifieke patiëntkarakteristieken en sneltesten te betrekken om zodoende eventuele voordelige effecten van behandelingen te kunnen voorspellen. Daarnaast dient onderzocht te worden of diagnostische instrumenten de aanwezigheid van een bacteriële infectie of inflammatie kunnen aantonen op ba-sis van onderzoek van het slijm van de neus en sinussen.

2) De bevindingen van dit proefschrift tonen aan dat corticosteroïden niet effectief zijn voor het behandelen van de algemene populatie van patiënten met ARS. Deze conclusie vormt aanleiding tot nieuwe hypothesen ten aanzien van de oorzaak van de klachten en symptomen. Theoretisch zouden de klachten zoals neus-verstopping en nasale afscheiding veroorzaakt kunnen worden door dysregulatie van het autonome zenuwstelsel van de epitheliale seromuceuze klieren. Zodoende zou remming van de overmatige slijmproductie van de seromuceuze klieren van de neus door het toedienen van intranasale anticholinergica kunnen leiden tot vermindering van symptomen. Nieuwe onderzoeken zouden daarom de effectiviteit van intranasale anticholinergica moeten vaststellen bij patiënten met klachten van ARS zonder dat daarbij sprake is van onderliggende chronische neusklachten en/of (niet)allergische rhinitis.

3) De huidige symptomatische behandelingen hebben geen bewezen voordelige effecten bij patiënten met ARS. Suboptimale symptomatische behandeling zou het onnodig voorschrijven van antibiotica of INCS in de hand kunnen werken. Daarnaast is het optimaliseren van de huidige symptomatische behandeling van groot belang om de zelfredzaamheid van patiënten te vergroten en de behoefte van de patiënten om een huisarts voor deze klachten te raadplegen te verminderen. In de Verenigde Staten en het Verenigd Koninkrijk wordt de neusholte van patiënten met neus- en bijholten klachten in toenemende mate gespoeld met een sinus irrigatie apparaat (bijvoorbeeld een netipot) om zodoende de overvloedige hoeveelheid slijm van de neus en sinussen te verwijderen. Een systematisch literatuuronderzoek naar het gebruik van irrigatie van de neus en aanliggende bijholten bij klachten van chronische rhinosinusitis toonde voordelige effecten van deze behandeling aan. Toekomstige studies dienen de effectiviteit van nasale irrigatie met een sinus irrigatie apparaat vast te stellen bij patiënten met klachten van ARS.

In dit proefschrift hebben we laten zien dat er op dit moment geen effectieve behandeling beschikbaar is voor patiënten met klinisch gediagnosticeerde ARS. Tot een dergelijke (preventieve) behandeling is gevonden, adviseren wij een sympto-matische behandeling (decongestieve neusdruppels en hoge dosering pijnmedicatie). Het implementeren van een dergelijk advies blijft echter een uitdaging gezien het hoge aantal voorgeschreven antibioticakuren en INCS preparaten. Wij denken dat het toepassen van een zogenaamd "shared decision making" model, waarin de huisarts de verwachtingen van de patiënt expliciet exploreert en tezamen met de patiënt de mogelijke behandelopties bespreekt, tot een vemindering van het aantal voorgeschreven antibioticakuren en INCS preparaten kan leiden.

Chapter 7

Summary

Samenvatting

Dankwoord

Curriculum Vitae

In dit laatste, ongetwijfeld meest gelezen, deel van mijn proefschrift wil ik graag van de gelegenheid gebruik maken om een ieder te bedanken die een bijdrage heeft geleverd aan het tot stand komen van mijn proefschrift, waarbij ik een aantal mensen in het bijzonder wil uitlichten.

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Chapter 7

Summary

Samenvatting

Dankwoord

Curriculum Vitae

Roderick Paul Venekamp was born on the 21th of June 1983 in Gorinchem, the Netherlands. In 2001, after graduating his secondary school at the Gymnasium Camphusianum in Gorinchem, he started his medical training at the Utrecht University. During this study he developed an interest for both clinical care and research of general practice, with a special interest for upper respiratory tract infections. After his graduation in 2008, he started to combine his GP vocational training with a PhD programme at the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht which he performed under supervision of Prof. dr. Marc J.M. Bonten, Prof. dr. Theo J.M. Verheij, Prof. dr. Maroeska M. Rovers and dr. Alfred P.E. Sachs. During this combined programme he also successfully finished a master programme Epidemiology Postgraduate at the Utrecht University Graduate School of Life Sciences.

At present, he is in his second year of his GP vocational training which he combines with a postdoctoral position at the Department of Otorhinolaryngology of the Division of Surgical Specialities and the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht with the objective to develop and supervise the conduct, analysis and report of clinical trials on the effectiveness of medical and surgical interventions for common ear, nose and throat conditions, especially in children.