Acute Rhinosinusitis (ARS). Diagnosis and treatment of adults in general practice.

Jens Georg Hansen

This review has been accepted as a thesis together with seven previously published papers by University of Aarhus 30th of May 2013 and defended on 29th of November 2013

Official opponents: Christian von Buchwald & Lars Bjerrum

Correspondence: Department, Rosenlunden 9, 9000 Aalborg, Denmark.

E-mail: jensgeorg@dadlnet.dk

Dan Med J 2014;61(2):B4801

THE SEVEN ORIGINAL PAPERS ARE

1. Hansen JG, Schmidt H. Danske praktiserende lægers diagnosticering og behandling af sinuitis acuta. Ugeskr Læger 1994; 156:1934-40.
2. Hansen JG, Schmidt H, Rosborg J, Lund E. Predicting acute maxillary sinusitis in a general practice population. BMJ 1995; 111:233-6.
3. Hansen JG, Højbjerg T, Rosborg J. Symptoms and signs in culture-proven acute maxillary sinusitis in a general practice population. APMIS 2009; 117:724-9.
4. Hansen JG, Lund E. The association between paranasal computerized tomography scans and symptoms and signs in a general practice population with acute maxillary sinusitis**.** APMIS 2011; 119:44-8.
5. Hansen JG, Schmidt H, Grinsted P. Randomised, double blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. Scan J Prim Health Care 2000; 18:44-7.
6. Hansen JG. The effect of acute rhinosinusitis on pulmonary function in adults. Prim Care Respir J 2009; 18:224-5.
7. Hansen JG. Management of acute rhinosinusitis in Danish general practice: a survey. Clin Epidemiol 2011; 3:213-216.

Introduction

Patients in general practice have more vague and diffuse symptoms and are often very early in the disease period, compared with referred patients to hospital and specialist practices. Patients are therefore more unselected in general practice, and the classic problems of diagnosing a vague defined disease will be more pronounced.

The probability of disease in general practice are lower, and patients often present only a part of the classic symptoms that make up the clinical picture, which also reflects that the reliability of the various test outcome is more uncertain than in patients at a specialized hospital department. In Table 1 it can be seen that, while the sensitivity and specificity is independent of the prevalence of the disease are the predictive values conversely extremely dependent of the prevalence.

Table 1. The relation between sensitivity, specificity, positive predictive value and negative predictive value. The diagnostic universe. N = 1000.

Test	+Disease	÷Disease	Total
Positive	a, true positive	b, false positive	a+b, all with positive test
Negative	c, false negative	d, true negative	c+d, all with negative test
Total	a+c, all with disease	b+d, all without disease	

Sensitivity = a/a+c
Specificity = d/b+d
Positive predictive value (ppv) = a/a+b
Negative predictive value (npv) = d/c+d
Given a disease in general practice has a prevalence of 10%, and the test has a sensitivity and specificity of 90%, the figures in Table 1 are as follows:
a = 90
b = 90
c = 10
d = 810
Then, the positive predictive value = 50%, and the negative predictive value = 98%. Conclusion: a bad test.
If the prevalence on the contrary is 50%, and we assume that the sensitivity and the specificity are unchanged, the following result will be:
a = 450
b = 50
c = 50
d = 450
This means that the positive predictive value = 90% and the negative predictive value = 90%. Conclusion: a good test.
Likewise, can various symptoms and signs predictive value of a given disease be calculated. If the disease has a low prevalence in the population, e.g. in general practice then the strength of symptoms and signs rank lower, than at the hospital, where there will be many more patients and most of these have more pronounced symptoms and signs than in general practice. For the physician working in the clinic, it is important to know the predictive values when the final diagnosis has to be decided, as it is just based on the result of the diagnostic test (1,2).

Definitions, pathophysiology and etiology.

The nasal sinuses include maxillary sinus, frontal sinus, ethmoid cells and sphenoid cells. Only maxillary sinus, and the ethmoid cells are developed at birth. Maxillary sinus is fully developed at 18 years of age. The frontal sinus is formed at 6-7 years of age and is fully developed at 16 years of age. The sinuses affect the

tone of the voice by serving as a resonance chamber. Acute sinusitis is both a common and frequent disease both nationally and internationally (3,4). Most frequently is ethmoid cells and maxillary sinus infected, often bilateral. Sinus ethmoidalis is more or less involved in a common cold, and there is a gradual transition to the actual sinusitis. Sinusitis frontalis is more rare and often unilateral. Sinusitis sphenoidalis only plays a minor role in practice, and it is rarely diagnosed. All sinuses can be infected simultaneously (pansinuitis) (5). Since the nasal mucosa is also involved in the inflammation, is it now generally agreed to call the disease acute rhinosinuitis (ARS) (4,6). The patients typically consult their general practitioner (GP) with a statement that they have sinusitis again, and that they have had it before. The challenge for the GP is in this situation either to agree with the patient - or provide a different diagnosis. A Dutch study showed that the GP was insecure of the diagnosis in approx. 30% of patients who were suspected of sinusitis maxillaris acuta (7). The latest statement of antibiotic use in general practice in Denmark is from 1987 (3). According to that study, the most common upper respiratory tract infection (URTI) was diagnosed among 15-44 years of age, which led to antibiotic treatment, tonsillitis acuta with 21%, followed by acute sinusitis by 17%. 90 % of the total oral antibiotic consumption in Denmark is prescribed in general practice. This means that the disease either is very frequent, or it is highly over diagnosed. Many specialists, allergologists, otolaryngologists, pulmonologists, paediatricians and general practitioners make the diagnosis of ARS. In an attempt to clarify the different diagnostic definitions, the task force behind the reference 4 in 2007 has reviewed the report published as reference 6, and latest in EPOS 2012 (8) and proposed new definitions of the disease used in epidemiological studies/general practice:
Common cold/acute viral rhinosinusitis is defined as: duration of symptoms for less than 10 days.

Acute post-viral rhinosinusitis is defined as: increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration.

Acute bacterial rhinosinusitis (ABRS) is suggested by the presence of at least 3 symptoms/signs of:
Discoloured discharge (with unilateral predominance) and purulent secretion in cavum nasi,
Severe local pain (with unilateral predominance)
Fever > 38°C
Elevated ESR/CRP
Double sickening (i.e. a deterioration after an initial milder phase of illness)

Pathophysiological there is an obstruction of the sinus ostium leading to reduced O_2 tension, increased CO_2 concentration and thus ciliary impairment. This causes obstruction of the normal drainage through the ostium and risk of bacterial growth in the sinus (9-11). The description of symptoms and objective signs associated with pus in the maxillary sinuses are often imprecise and mostly based on studies in selected patients (10,12-14). The clinical picture in general practice is recently described in detail, and has revealed important differences between signs and symptoms, compared with the clinical picture, as it is in patients referred on to the ear-nose-throat (ENT) doctor, the vast majority of patients in general practice have the disease to a lesser degree (7,15 to 23). Under normal conditions, the maxillary sinuses are the only sinuses, which are accessible to antral aspiration (14,18,24).

Alternative studies of the sinuses are: X-ray, ultrasonography, CT and MRI scanning. CT and MRI are the two best methods in terms of accuracy to detect pathology in the sinuses. CT is superior to conventional radiography for detecting pathology since the examination provides more detail. Ultrasonography can be used in the primary sector, but requires knowledge and experience of the examining doctor to interpret the results. Detection of a fluid level is in line with the X-ray. The imaging diagnostic studies are, however, subject to the uncertainty that a fluid level or opacification not only can be caused by pus, but also serous or mucopurulent secretions (7,25-39). Blood tests performed as near-patient testing to assess the severity of infection, includes C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (18,22,29,40-43). The question if allergy predisposes to ARS has been evaluated in several studies on the theory that an oedema of the mucosa of the osteomeatale complex may cause obstruction of the sinus ostium reducing the ventilation, leading to mucus retention and thereby increase the risk of bacterial invasion (8,44-48). However, there are to date no reliable studies to confirm this hypothesis (6).

The etiology of ARS can be divided into acute viral rhinosinuitis and acute bacterial rhinosinuitis often preceded by a viral rhinitis or common cold (8,49,50). In our study we could not demonstrate that acute maxillary sinusitis were more frequent in patients with preceding catarrhalia (18). Pitkäranta found in patients with acute sinusitis rhinovirus in 7 out of 14 maxillary sinus (51). Evans rhinovirus found in 2 out of 32 maxillary sinus (52), and Hamory detected virus in 11 out of 70 maxillary sinus (6 rhinovirus, 3 influenza A and parainfluenza in the last 2) (53). The three references are based on maxillary sinus puncture. Other works dealing with viruses and ARS are based on nasopharyngeal swabs and from the osteomeatale complex (54,55). It is not known with certainty how the bacterial invasion of the maxillary sinuses occurs during a viral infection, but sneezing, coughing and nose blowing causes pressure differences between the cavum nasi and sinus so that the bacteria in the nasal secretions probably can invade sinus (55). An odontogenic sinusitis can occur if an infection arising from dental sources breaks through to the maxillary sinus, or if, in connection with a tooth extraction occurs perforation of the sinus (5). Approximately 10% of sinusitis maxillary is of odontogenic genesis (56).

The etiology of the bacterial infection is commonly *Streptococcus pneumoniae* (*S. pneumoniae*) and *Haemophilus influenzae* (*H. influenzae*), which together accounts for approx. 50% of the isolated bacterial species in pus obtain by lavage or aspiration (8,18,22,43,57-66). However, it is also worth noting that in up to 30-40% is the bacteriological culture negative (63). The etiology of the culture-negative cases is not clear, but undoubtedly many are due to viruses or rare bacterial species. Another theory that has been put forward is that the procedure by maxillary sinus puncture (aspiration or lavage) results in diluting and oxygenation of the material, which may result in a reduction of the amount of bacteria in the sample. Finally, it is argued that lidocaine and noradrenaline, which are used in local anaesthesia, are bacteriostatic especially against *S. pneumoniae.*

Differential diagnosis
A number of other conditions should be considered as possible differential diagnoses: Purulent rhinitis, myogenic/neurogenic facial pain, joint dysfunction (often unilateral), and allergic rhinitis

in the pollen season. Benign tumours, polyps and osteomas only play a minor role. Malignant tumours especially develop in the maxillary sinus, less often in ethmoid cells, and almost never in the frontal sinus and sphenoid cells. The most common type is squamous cell carcinoma that accounts for 2/3; the rest is made up by adenocarcinomas and sarcomas. Symptoms are nasal congestion, rhinorrhea and pain accompanied by purulent or bloody secretion from the nose (5). Cancer in the sinuses is rare, and was not diagnosed in the study. During the time period in which this material was collected, the incidence of cancer in the sinuses was in 1992, 93 and 94, respectively 11, 23 and 33 new cases, according to the Danish National Patient Registry. Up to and including 1993 was used ICD-8 code: 16 029, from 1994 ICD10 code: C 31.0

Is ARS a female disease?

The disease is found more frequently in women than men (9,18,19,21,67). In the Cochrane review from 1999 (68) that included 7,330 patients, were 55% women. This gender difference may be caused by selection bias because women more frequently than men consult the doctor (19,21). In the KOS study (Contact and Epidemiological Pattern Survey) from 2010, were the proportion of women and men respectively 62% and 38%, 46 women of the fertile age was diagnosed with acute sinusitis versus 21 men (69) (Table 2). The pathogenesis of the gender difference is not fully understood, but hormonal conditions, allergies and the fact that women are more often together with small children at home, at work and in child care centres, increasing the risk of child-to-adult infection (19). Studies have also shown that pregnant women have more often rhinitis/sinusitis than non-pregnant women (70,71). Studies have not shown a clear relationship between estrogen/progesterone concentrations during pregnancy nor in relation to the menstrual cycle, however, there are several works that suggest that the production of placental growth hormone is involved in the development of gestational rhinitis/sinusitis, just like smoking and allergies to dust mites are probably risk factors (71-75). The relationship between hormonal contraceptives and ARS has not been studied.

Table 2.

Age groups	Gender distribution in KOS 2008		Contacts with sinusitis diagnosis		
	Men %	Women %	Men (%)	Women (%)	Total
0-14	51	49	1 (33)	2 (67)	3 (100)
15-30	31	69	2 (15)	11 (85)	13 (100)
30+	38	62	19 (35)	35 (65)	54 (100)
All	38	62	22	48	70

Source: Kontakt - Sygdomsmønsterundersøgelse KOS 2008. Forskningsenheden For Almen Praksis og Afdelingen for Almen Medicin, Aarhus University, Denmark

Background

Inflammation of the nasal sinuses is frequently occurring. When the literature is searched , there is a differentiated picture of the nature of disease and severity. When the disease is evaluated from the otological point of view, it is characterized by malaise, fever, and pus in the nasal cavity, pronounced facial pain predominantly unilateral, reduced or loss of smell, increased ESR and or CRP and a disease duration of up to 10 days or worsening after 5 days and less than 12 weeks duration. This is the conclusion of EPOS 2012 (8). However, according to this thesis a somewhat different clinical picture is found in general practice with a predominantly milder disease, both in terms of symptoms and signs and a somewhat faster disease course. The survey of 1991 - published in 1994 - was inspired by a random survey of GPs, how they diagnosed ARS, how they evaluated symptoms and signs, which treatment they used, and a relevant question about their own certainty if they had made the correct diagnosis (76). Literature studies in the survey revealed at the time that studies in unselected patient materials from general practice were more or less missing to illustrate symptoms and signs predictive values of pus in the sinuses (77,78). Today we would have used the term evidence-based knowledge.

The thesis is based on an evaluation of the replies to the questionnaire continued in a prospective study of how GPs diagnose acute maxillary sinusitis in order to establish reliable diagnostic criteria to the following reference standards: Diagnostic sinus puncture CT and bacteriological diagnosis. It is debatable whether antibiotic treatment of ARS have any effect on the cure rate (79-95), therefore, there is also included a randomized, double – blind, placebo-controlled trial of penicillin V. The concept of United Airways covers the hypothesis that airway epithelium is similar in both upper and lower respiratory tract, and therefore there is a close relationship between diseases of the upper and lower respiratory tract (96-104). This is evaluated in the study where the lung function were examined during and after an ARS in lung healthy and non allergic patients. Finally, I have through a questionnaire assessed how the later years of information and debate on diagnosis and treatment of ARS, have affected the GP's management of he disease up for today.

Aim

Much of the uncertainty about the disease is probably due to the fact that the patients examined and treated in general practice have the disease in a lesser degree, compared to the patients treated by a medical specialist and the hospital, where the majority of our knowledge comes from. I therefore wished to describe this large group of patients in general practice, and establish evidence-based guidelines for diagnosis and treatment in particular the issue of antibiotic treatment on the basis of the following works: Firstly, how GPs diagnose and treat ARS based on a questionnaire (article 1). Secondly, to investigate the diagnostic value of the described symptoms and signs, and the use of paraclinical examinations in a prospective study with reference to, respectively: sinus puncture, microbiology, and CT (articles 2, 3 and 4). Thirdly, to investigate the effect of antibiotic treatment in a randomized, double blind, placebo-controlled trial with penicillin V (article 5). Fourthly, to investigate the effect of ARS on pulmonary function in adult patients without chronic lung diseases or allergy (United Airways) (article 6). Fifthly, to assess whether the later years of debate on the diagnosis and treatment of the disease has had an impact on the GPs' management of ARS (article 7).

Material and methods

300 general practitioners, who were representative in relation to geographical location, gender and candidate age, were invited to participate in the first survey (article 1). The clinical study (article 2) are based on patients aged 18-65 years suspected of acute maxillary sinusitis either reason for encounter or after the doctor's examination. This study included 8 general practices. Patients were included consecutively and only once. These are the same patients as were analysed and described in article 3-4. In the treatment study (article 5) attended 26 general practices. The patients were aged 18-65 years. They were included consecu-

tively and only once. Article 6 describes the association between ARS and the lung function defined by changes in FVC, FEV1, F25-75 and PEF. The patients ranged in age from 18 years and up. For the final study, 300 randomly selected general practitioners were invited. The studies are all done in general practice both in North Jutland and on Funen partly in collaboration with the department of Ear Nose and Throat Surgery, the department of Neuro Radiology, the department of Clinical Microbiology Aalborg Hospital and Aarhus University Hospital and department of Clinical Epidemiology Aalborg Hospital and Aarhus University Hospital.

The statistical methods used are described in detail in each original article. For the analyses have over the years been used SPSS and MiM computer software and EXEL spread sheet (105,106). The statistical calculations were performed partly by Biostatistics, University of Aarhus, Centre for Health Statistics, department of Mathematical Sciences, Aalborg University, and Centre for Cardiovascular Research, department of Cardiology, Aalborg Hospital, Aarhus University Hospital.

CT scan

CT scans were performed at the Neuro Radiology Department with 10 mm thick cuts, which were an accepted method for the examination of the sinuses when the project was planned in 1992. Since at that time one could not change the KV and mAmp in the CT scanner (which can be done in modern scanners to day), the only way to reduce radiation dose was to make the cuts thicker. In short: Fewer cuts, fewer rays. If you made 2-3-mm thin cuts such as for example at some studies of the brain, the CT-radiation dose would be much higher than for conventional X-rays of the sinuses. The information at the 10 mm wide cut through the sinuses was by general accepted at that time and also sufficient to see what you wanted in connection with suspected benign disorders, and thus more informative than plain radiography. If the CT showed suspected tumour or other unresolved pathology, one could supplement the examination with a thinner cut. 10 mm cuts through the sinuses were good standard at the time. That we did not consciously make the cuts up through the sinus frontalis was because it was the maxillary sinus we were interested in visualizing prior to any sinus puncture as we because of ethical reasons, chose not to puncture a maxillary sinus if CT showed neither mucosal swelling nor fluid level or opacification. In that way we held the radiation dose as low as possible. The modern scanners are far more radiation hygienic and can be used without problems in a much more detail visualizing way.

Sinus puncture

The sinus puncture was performed at the department of Otorhinolaryngology as described below. There were no recorded serious adverse reactions to the puncture. Initially the nose was sucked clean. The local anaesthesia was performed as follows: A solution of 10% lidocaine and 1% of norepinephrine on cotton wool was applied to the posterior part of the meatus medius, and meatus inferior. After topical anaesthesia an infiltrative anaesthesia with a solution of 2% lidocaine and 0.5 % norepinephrine was injected under the mucous membrane of the nasal cavity lateral wall of the inferior concha. The puncture was performed with a 1.4 mm lumbar needle approx. 1.5 cm behind the front part of the concha inferior with the direction laterally and slightly upwardly and rearward. In all cases, there was firstly attempted aspiration of secretion through the needle with attached syringe. If there was hereby-aspirated pus then the material was collected on a sterile charcoal-coated cotton swab. If no material could be aspirated spontaneously, irrigation was performed with 50-100 ml. 0,9% saline solution and consequence re-aspiration was performed with the patient's head bent forward to allow the irrigation material to be collected in a sterile bowl (i.e. lavage). The irrigation material was also collected on a sterile charcoal-coated cotton swab, and placed in a glass tube with Stuarts transport medium and sent to the Department of Clinical Microbiology for bacterial culture.

Microbiological procedures

The specimens were plated on 5% horse blood agar with a staphylococcus streak and on chocolate agar (both incubated for 48 hours at 35 °C in 5% CO_2), on MacConkey agar (incubated for 48 hours at 35 °C in ambient air) and on 10% horse blood agar with a 5 µg metronidazole disc (Oxoid, Cambridge, UK) (incubated 48 hours at 35 °C in an anaerobic chamber). For S. *pneumoniae,* the diagnosis was confirmed by capsular swelling (OMNI serum, Statens Serum Institut, Copenhagen, Denmark). *H. influenzae* was identified by typical colony morphology, including satellism around the staphylococcus. Strains with atypical colony morphology were tested for the X - factor requirements by the porphyrin test. Other species were identified according to standard methods.

In the aspirates were pathogens without contaminated nasal flora in 61 %, while this was the case in 37 % of the irrigation material. In addition, pathogens mixed with nasal flora in 6% of the aspirates and in 20% of the irrigation material, in total numbers of pathogens were found in 67% of the aspirates and in 57% of the irrigation material (p = 0.39 *). Nasal flora was found in 17% of the aspirates and in 44% of the irrigation material (p = 0.006 *). 22% of aspirates and 19% of the irrigation material showed no growth (p = 0.91). In 9 % of the aspirates and in 9% of the irrigation material was detected co-culture with a mixture of 2 or more pathogens. (*P values calculated by Fisher 's exact test)

No wonder that the irrigation material more than the aspirates were contaminated with bacteria from the nasal cavity, but in both types of samples were the contamination of minor and non-dominant quantity in the case where there also were pathogens. It can not be excluded that in samples with contamination in quantities of some or more colonies (7 irrigation material and 2 aspirates) may pathogens have hidden themselves in smaller quantities, which partly could explain that there were 44% of the irrigation material without pathogenic and 38% of aspirates. The fact that 22% of aspirates and 19% of the irrigation material were completely without growth can be caused by the fact that the anaerobic culture was hardly optimal at the time of collection. We only found anaerobic growth in 1 irrigation material and in no aspirates. The samples were incubated aerobically and anaerobically for 2 days, and many anaerobic bacteria will take longer to grow. It was not at that time routine to examine the anaerobically cultured plates with UV light. Anaerobic cultivation for 4 days followed by inspection under UV light would probably have led to the discovery of several anaerobic bacteria. This was supported by the fact that in several samples were described that there were smelly purulent secretions, but the culture showed no growth.

Some respiratory viruses could be grown at the time the survey was conducted, but it took a long time and was not routine. We did not have the opportunity to culture the virus in Aalborg, but SSI (Statens Serum Institut, Copenhagen) had some techniques for testing. Only after alternative methods (e.g. antigen-antibody

reactions) became common, the virus detection started, but it was not until PCR was widespread that virus diagnostics in respiratory infections became routine. As it was not possible to treat virus infections at that time, the subject was not prioritized. Pathogen-susceptibility testing on the cultures was performed. All tested *S. pneumoniae* and haemolytic group A streptococci were fully sensitive to penicillin, all *H. influenzae* were fully sensitive to ampicillin. With the exception of 1 were *S. aureus* penicillin resistant, but full sensitive to meticillin. Among positive cultures with Moraxella catarrhalis (n = 4) 2 were tested, showing 1 penicillin-resistant and 1 full sensitive to penicillin.

Bias

In the survey (article # 1) is a response rate of 67 after sending out of the questionnaire and one reminder. A drop of 33% means that there is the potential for selection bias. This means that the group of GP's who responded to the questionnaire are not necessarily representative of all GP's. I will assume that the answers come from doctors who specifically are interested in the disease, but of course this is only an assumption, since non- respondents are not asked why they have not answered the questionnaire. On the other hand, the purpose of the questionnaire survey was to clarify how general practitioners evaluates signs and symptoms when they have to make the diagnosis supplemented by the reference choice of paraclinical examinations and treatments. Symptoms and signs are taken from textbooks in ear nose and throat diseases, and selection bias can at the most reprioritize the weighting of symptoms and signs. These signs and symptoms were used to define the choice of method in article 2 independent of the order of priority in the questionnaire. That we also asked for the doctor's diagnostic certainty is a natural part of the handling of the disease. When the general practitioner specifies a diagnostic certainty of 70%, it means that the doctor expects to make the correct diagnosis in 7 of 10 patients. A comparison the diagnostic accuracy in patients with AOM offers a higher diagnostic certainty, due to the eardrum can be visualized, while one can not look into the sinuses (17). Data in articles 3-4 are based on patient material described in article 2. In total, 282 patients were included. 77 were excluded before the study, of which 53 did not want to participate. The patients did not differ from those who completed the study with regard to age and sex, whereas there were not recorded symptoms and signs, and neither were measured OR nor CRP. Probably the patients had only had mild symptoms, and the influence on the final result is therefore considered of minor importance. During the study 31 did not want to continue and were excluded. They did not differ significantly from those patients who completed the entire study, with respect to age, sex, symptoms, signs, and results of SR and CRP. The same radiologist evaluated all CT scans, and the same otologist performed 70% of the maxillary sinus puncture. There could be bias in the reading of CT and to determine this, we should have made an inter- and intraobserver variation study in order to assess the reproducibility of the readings, which we did not do. The same may be true for the assessment of pus or mucopus in the aspirate and irrigation material in the maxillary sinus puncture. Overall, I believe, however, that one cannot attribute bias great importance for the interpretation of the results, as both the radiologist and otologist both were very experienced specialists. The randomized treatment study included 167 patients. 28 were excluded prior to randomization. They did not differ from those patients who were randomized. After randomization, an additional 6, 2 in the placebo and 4 of the group of penicillin excluded due to non-compliance. 6 patients, 3 in each treatment group discontinued treatment within 7 days. They were included in the analyses until dropout. With the choice of method we discussed in detail how we could control compliance and consumption of painkillers. We did not find that it was a reliable method that patients had to dispose of the medicines packaging at the control visit, since the empty packaging did not exclude that the patient had not taken the full dose, which was agreed. With regard to the consumption of analgesic treatment, we concluded that it would be difficult to control the consumption when it can be sold over the counter. Conversely, we concluded that if there were an uneven consumption in the 2 treatment groups, it would be most likely that the highest consumption would be in the placebo group, and it would lead to greater risk of type 2 errors. Finally, it should be pointed out that there was a significantly greater decrease in CRP levels after treatment with advantage to penicillin, which strongly speaks for an effect of penicillin. In the final survey differs the group of non-responders not from responders with regard to practice type or gender. I therefore assume that the management of the disease is similar in the 2 groups so that the risk of selection bias due to the relatively low number of responses are assumed to be small. The response rate of 50% also means that it can be difficult to generalize the answers, but on the other hand, there seem to be a certain accordance with the first answers, which suggests that the attitudes to ARS has not changed significantly over the years

Results and discussion

The following presents the results and discussion of each of the seven published articles. At the end of the section the results and discussion of the whole material is presented, followed by a conclusion, perspectives and summary.

Article # 1:

Diagnosis and treatment of acute sinusitis in general practice in Denmark.

The aim of this study was to evaluate the GP's weighting of symptoms, signs and use of paraclinical investigations for the diagnosis of acute sinusitis in adults and highlight what treatments they select to use.

A questionnaire was sent to 300 GPs, and after 3 weeks one reminder. They were representative in terms of geographical distribution, gender and candidate age. The response rate was 67%.

The questions were based on the usual signs and symptoms of sinusitis acuta as described in text books (5).

The clinical examination included examination of the ear, nose and throat, as well as palpation of the facial area and was used in 100 %, while the X-ray examination, pharyngeal swabs and measuring the erythrocyte sedimentation rate (ESR) was used in 10%, and leukocyte count was used in 5 % of the consultations. The CRP analysis was not available at that time as a near -patient test. The GPs' assessment of their own diagnostic certainty was 70 % (95 % CI 70-75%). This statement should be interpreted, as the doctor believes to provide the correct diagnosis in 70 % of the cases, or im other words that the doctor expects to make the correct diagnosis in 7 of 10 patients.

When differences in methodology and analysis of published studies are taken into account, the picture of the following symptoms related to ARS is: Nasal congestion, purulent rhinorrhea, unilateral pain over the maxillary sinuses, prior catarrhalia, facial pain, maxillary toothache, decreased sense of smell, and the following objective findings: purulent secretions over the inferior concha,

purulent secretion in the pharynx back wall and nasal polyps. For comparison the doctors weighted in this study pain and tenderness over the sinuses at the most followed by pain bending forward, pain in the maxillary teeth and previous catarrhalia. In addition, oedema of the sinuses and tenderness on tapping the maxillary teeth. This means that the GPs' are weighting pain higher than the detection of purulent secretions in the nose, which is in line with a Norwegian study (17). For comparison evaluates ENT specialists' purulence and pain alike in the diagnosis of ARS. This may be due to that the GPs meet the patients earlier in the disease process than the ENT specialists and at a time when purulence is not yet developed (17). The most frequently used treatment is decongestants nose drops / spray and in half of the cases were also used antibiotics, of which penicillin V was 70 %. A questionnaire entails a risk that the doctors answer from general considerations, which do not necessarily reflect the daily clinical procedure (107). This study does not answer this question. Furthermore, the problem of selection bias is discussed above.

Article # 2:

Predicting acute maxillary sinusitis in a general practice population.

The aim of this study was to investigate the diagnostic value of symptoms, signs, CRP and ESR in order to establish a clinical criterion of acute maxillary sinusitis. 174 patients were included in the study. The median age was 35 years. 67% were women. Patients were after an examination (the examination was similar in all the general practises using a standardized form) by the GP admitted to a CT (computer tomography) of the maxillary sinuses within 24 hours. If the CT showed mucosal swelling and or fluid the patient was immediately referred to a puncture of the maxillary sinus. Both studies took place at Aalborg Hospital. The reason why we chose to CT scan all the patients was that a normal CT scan with very high probability could exclude pathology in the sinuses (30). For ethical reasons we did not want to expose the patients for a subsequent puncture of the maxillary sinuses, why only the maxillary sinuses, on which changes were detected on the CT were aspirated.

If the aspirate or the antral lavage contained either purulent or mucopurulent material, the patient was diagnosed as having acute maxillary sinusitis. Any purulent or mucopurulent material obtained was sent to the department of microbiology for bacterial culture. 70% had abnormalities on the CT and on 53 % were detected purulent or mucopurulent material in the subsequent puncture of the maxillary sinus. Patients who were referred to sinus aspiration had a disease duration of 7 days (median value, quartiles 5-14 days, range 1-28 days). Pathogenic bacteria were found in 66% of the cultures (most commonly *S. pneumoniae* and *H. influenzae*), negative culture in 22%, and missing cases 12%. 95% of the patients had maxillary sinus pain. The univariate analysis showed that only unilateral maxillary pain and maxillary toothache and unilateral tenderness over the maxillary sinuses was significantly associated with pus in the maxillary sinuses. The patient's statement that they had previously had had acute maxillary sinusitis was significantly negatively associated with pus in the maxillary sinuses. CRP values >10 mg/l and ESR value in men > 10 mm/h and > 20 mm/h in woman was also significantly associated with pus in the maxillary sinuses. There is a dose-response relationship between the result of CRP, and presence of purulent maxillary sinusitis, whereas the correlation between the ESR values and purulent maxillary sinusitis is less pronounced. There may be several explanations for this. Firstly, CRP is an acute phase reactant, which is very sensitive to a stimulus in contrast to ESR, which is slower and, therefore, needs a longer time to react, and it also takes longer time to normalize after the infection. Another explanation may be that ESR is not particularly sensitive to the infection in the sinuses, in contrast to CRP. In the section of discussion, I have evaluated the importance of ESR in the clinical criterion. Subsequently a multivariate analysis was performed, which showed that CRP and ESR were the only variables independently and significantly associated with pus in the maxillary sinuses. The results confirm that the disease is over-diagnosed if the GP only use the usual and generally accepted diagnostic criteria . A combination of ESR and CRP showed a sensitivity of 0.82, specificity of 0.57, positive predictive value (ppv) of 0.68 and negative predictive value (npv) of 0.74. On the basis of these findings, we have defined a clinical criteria for acute maxillary sinusitis: Pain over the maxillary sinuses either unilaterally or bilaterally in combination with either the CRP value > 10 mg/l and/or ESR value for men > 10 mm/h and > 20 mm/h in women. Despite the fact that the predictive values are not optimal, respectively, a ppv of 0.68 and a of 0.74, then it is a better basis to diagnose the disease than based on the clinical findings. Using this criterion 32% of the patients are over treated, as opposed to approx. 50% if the doctor only base his diagnosis on the clinical picture.

The disease is diagnosed most frequently in the younger age groups. More than 2/3 of the patients are women and this gender difference is also found in other studies (22). The reason for this gender difference has not been established with certainty.

Article # 3:

Symptoms and signs in culture-proven acute maxillary sinusitis in a general practice population.

The purpose of the study was to evaluate signs and symptoms in patients with acute maxillary sinusitis and a bacteriological diagnosis. The study is a continuation of the study presented in article # 2, where symptoms and signs were based on the diagnostic gold standard: Purulent or mucopurulent secretions macroscopically assessed by maxillary sinus puncture. In this study, the aim was to evaluate the same parameters in patients where there were a demonstrated growth of either *S. pneumoniae* or *H. influenzae* that are the two most frequently isolated bacteria from the sinuses in the context of an acute infection. Temperature> 38 °C and maxillary toothache were significantly associated with the presence of either *S. pneumoniae* or *H. influenzae*, and increasing values of ESR and CRP (cut-off values: CRP values>10 mg/l and ESR value for men > 10 mm/h and women >20 mm/h) was significantly associated with positive growth. None of the other investigated symptoms and signs were particularly sensitive to a specific bacteriological diagnosis. All the patients complained of pain in the maxillary sinuses, but there were no correlation between the patient's indication of which side there was pain, and the uni- or bilateral infection with either *S. pneumoniae* or *H. influenzae*. The same was true regarding tenderness over the maxillary sinuses, where it was not possible to demonstrate a relationship between uni- and bilateral - or absence of tenderness OR 0.2 (0.02 -1.5) and OR 0.8 (0, 05-12).

The study confirmed that the most common bacteria in acute maxillary sinusitis are *S. pneumoniae* and *H. influenzae*, 23% and 15%. Furthermore, there are calculation errors in Table 5 in the original article. The corrected table is inserted here. In the column "Absent" CRP is missing in 1 patient.

Table 5. Acute maxillary sinusitis. The association between the concentration of C reactive protein (CRP) and the results of culture for *Streptococcus pneumoniae* or *Haemophilus influenzae* from either one or both maxillary sinuses in 45 patients with acute maxillary sinusitis compared with 82 patients with an absence of acute sinusitis.

CRP mg/l	Unilateral N	Bilateral n	Absent n	OR (95 % CI)
<11	8	4	49	
11-49	10	7	24	2,89(1,77-4,73)
>49	11	5	8	8,17 (3,81-17,53)

Haemolytic streptococcus group A is not included in the analysis because the epidemiology of this bacteria showed large variations in time when the study took place (108). *Moraxella catarrhalis (Branhamella catarrhalis)* were found in a relatively low frequency and can be explained by the fact that it is most common in children (109), who were not included in this study. *Staphylococcus aureus* accounted for 5.3% of the isolates, but several authors consider this bacteria to be contamination from the nasal cavity (58). Similarly, the proportions of anaerobic isolates are low compared to other studies (59,62). In 44% of patients failed to detect bacteria in the aspirate. It is also shown in other studies, where the proportion varies between 5-42% (59-62,65,66). Again, we found that the patients own statement on previous maxillary sinusitis was significantly negatively associated with the growth of *S. pneumoniae* and *H. influenzae*.

Article # 4:

The association between paranasal computerized tomography scans and symptoms and signs in a general practice population with acute maxillary sinusitis.

CT is usually the preferred diagnostic test because the examination may show even minor pathological changes in the sinuses. On the other hand, there are also studies that question the association between sino nasal symptoms and findings on CT by ARS (26,34). The aim of this study was to evaluate the association between symptoms and signs with changes on the CT of the maxillary sinuses. The study is a continuation of articles 2 and 3. If the doctor suspects acute maxillary sinusitis based on the clinical examination, the patient was acute referred to CT within 24 hours. CT was performed in order to detect changes in the maxillary sinuses. The following scoring system was used for the evaluation of the pathological changes. Mucosal swelling: None (= 0), moderate (= 2) and massive (= 3). Fluid level: None (= 0), moderate (= 2), and total opacification (= 3). Scores were calculated for 2-6, where 6 represented the most pronounced changes. Patients with score = 0 were diagnosed as healthy and did not continue in the study, while all others were further referred to sinus puncture. 122 (70%) had changes on CT. 45% had unilateral changes, 55% bilateral changes. In 78 patients were the ethmoid cells were also identified on the CT, and of these 79% had abnormalities. The sphenoid cells were identified in 21 patients, and of these, 57% had abnormalities. The frontal sinus was not identified in any patients. The strongest association with pathology on CT was purulent nasal discharge, unilateral oedema over the maxillary sinus, and preceding URTI. Self-reported previous sinusitis was significantly and negatively associated with maxillary sinusitis. To investigate the association between the severity of changes on CT and the clinical picture, we stratified the material into two classes: Score 5-6, or < 5. Based on this approach we found the strongest association with purulent nasal discharge (p = 0.02), preceding URTI (p = 0.06), maxillary toothache (p = 0.10), and oedema over the maxillary sinuses (p = 0,10). There was a strong association between increasing values of CRP and ERS and the changes on the CT (n=187). It was not possible from the CT to determine whether the infection was caused by *S. pneumoniae* or *H. influenzae*. We were not able to demonstrate an association between unilateral or bilateral changes on CT and unilateral or bilateral pain. The overall assessment of CT in the diagnosis of acute maxillary sinusitis shows that it can reduce the number of suspected maxillary sinus infections by 30% compared to the clinical diagnose (18). On the contrary, it does not seem realistic to implement CT in the daily clinic, because there will be waiting time for the examination in the hospital, and also economic costs involved.

Article # 5:

Randomised, double blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice.

The aim of the study was to evaluate the effect of penicillin V in adult patients with acute maxillary sinusitis in general practice. The study was randomized, double blind and placebo-controlled. 26 general practitioners participated. The clinical evaluation was based on the patients statements about pain intensity and degree of sense of illness the latter includes symptoms of nasal obstruction, nasal discharge and general discomfort. The patients scored pain and sense of illness on a scale from 0 to 5, where 0 = no pain or sense of illness and 5 maximum pain and sense of illness in a diary each day and the scoring began the day after start of treatment. The initial score was also recorded along with the duration of symptoms before starting the treatment. CRP and ESR were measured at the start and at end of the treatment. The patients were randomized to either treatment with penicillin V 1333 mg twice daily or placebo. 133 were randomized to treatment, penicillin V = 71, placebo = 62. During the study, 6 patients were excluded. They were included in the analyses until dropout. The study showed that treatment with penicillin V makes the patients painless faster than placebo. Three days after the initiation of treatment, the pain score was significantly lower in the penicillin group, but only in patients with a pain score above 3. After 7 days of treatment, the therapeutic gain = 34% as 71 % have recovered completely in the penicillin group versus 37% in the placebo group. From these figures one can calculate the number needed to treat is 2.9 (1/0.34). However, there was no significant difference between the penicillin and the placebo groups in terms of sense of illness. At the end of treatment, 88 % of the patients had achieved normal CRP in the penicillin group compared with 75% in the placebo group ($p < .05$). However, there was no significant difference in ESR values. The empirical choice of penicillin V as the first drug of choice treatment is justified and in accordance with the Scandinavian recommendations. Pathogen-susceptibility testing were performed on the cultures. All tested *S. pneumoniae* and haemolytic group A streptococci were fully sensitive to penicillin, all *H. influenzae* were fully sensitive to amoxicillin. We have in this study chosen to use one of us previously defined clinical criteria, where the objective study of the ear, nose and throat region is supplemented by a blood test for determination of CRP and or ESR. Both tests are used in a near-patient-test design. CRP is in another study found both robust, accurate and correct in general practice, compared with results from laboratories (110). Increased values of both CRP and ESR are usually considered good predictors of a bacterial infection. In this study, there were relatively low levels of both CRP and ESR which could be explained by

the fact that the patients in general practice are less sick. The study shows that by using the clinical criteria and a relatively simple and inexpensive laboratory test, the doctor gets a good tool to either explain to the patient why penicillin is not indicated, or what the patient might expect if there is indication for treatment with penicillin (111,112). This is in line with that patients are more interested in the best treatment, and not so much in the correct diagnosis (113).

Article # 6:

The effect of acute rhinosinusitis on pulmonary function in adults.

The aim of this study was to examine how ARS affects the lung function in lung healthy adults. The study was observational. 25 patients with clinical symptoms of ARS defined by unilateral or bilateral maxillary pain, purulent secretions in the nose and an elevated C-reactive protein (CRP) value above 10 mg/l and no evidence of chronic lung disease or a history of allergy were included consecutively and only once in the study. Exclusion criteria were acute lower respiratory tract infection, recurrent ARS, asthma, COPD, allergies or a chronic disease that could provide increased value of CRP, duration of symptoms beyond 4 weeks, pregnancy and unwillingness to participate. Exclusion criteria were based on interviews with patients and review of their medical records; all participants were patients in my clinic. None of the patients had symptoms or signs of acute lower respiratory tract infection. The patients were asked to return to clinical control 8 weeks after the primary visit. CRP was measured with near-patient testing in the clinic. Spirometry was performed with Vitalograf PFT II printer. The best of three reproducible time/volume curves were used as the patients lung function. The following parameters were measured and corrected for BTPS: Forced vital capacity (FVC), forced expiratory volume in the first second of a maximal expiratory manoeuvre (FEV1), maximal mid expiratory flow from 25-75 % of FVC (F25 -75) and peak expiratory flow (PEF). The study was performed according to the ERS criteria (114). Normal values were derived from the Danish Society of respiratory Medicine (115). Patients were asked to record in a diary how many days they had facial pain after the first visit. 8 weeks after the patient came back for a control visit where the pain score and CRP were recorded and spirometry was repeated. The variables FVC, FEV1, F25-75 and PEF showed normal distribution (Wilk-Shapiro test).

F25-75 and PEF were significantly improved between the first and second visit, whereas no difference was found in the values of FVC and FEV1. We found a significant association between CRP and F25-75 ($r = 0.65$, $p < 0.05$), but not with PEF ($r = 0.29$). There was also found a significant correlation between the changes in F25-75 and PEF ($r = 0.75$, $p < 0.05$), whereas no association has been demonstrated between pain score and F25 -75 ($r = 0.16$) or PEF ($r = 0.08$). Prescription of antibiotics had no effect on the results.

The study revealed (Table 3), that ARS is accompanied by a transient, but significant decrease in lung function evaluated on the F25 -75 and PEF, possibly caused by inflammation of the small airways or via a reflex mechanism that leads to an obstruction of the small airways and air- trapping. The reason that no changes were observed in FVC and FEV1 might be explained by the fact that the two parameters are not very sensitive predictors of small airway disease. The literature contains no information on the identified findings in this study. Further studies are recommended to further illustrate the results found.

Table 3. Differences in the pulmonary function variables (median values in litres) between initial (first) and final (second) visit. 95 % confidence intervals given in brackets.

Variables	First visit	Second visit	P value
FEV_1	3.4 (2.9-3.6)	3.4 (3.1-3.7)	ns
FVC	4.2 (3.8-4.5)	4.3 (3.8-4.6)	ns
FEV_1 /FVC	81 (77-83)	82 (77-84)	ns
F25-75	3.1 (2.7-3.7)	3.6 (3.0- 4.1)	0.009
PEF	413 (363-471)	485 (410-526)	0.03

Ns= non significance

Article # 7:

Management of acute rhinosinusitis in Danish general practice: a survey.

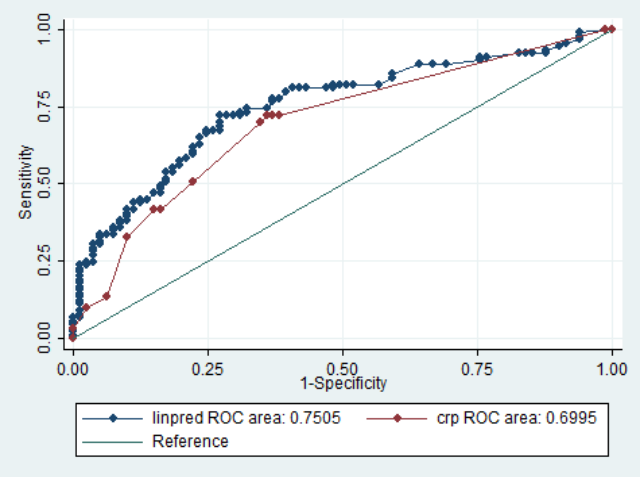
There has over the years been an increasing focus on diagnosis, use of CRP near -patient testing and the use of antibiotics. To evaluate whether this increased debate has had an impact and possible changes in GPs' approach to ARS diagnosis and treatment, the aim of the study to evaluate GPs prioritization of symptoms, signs and the use of paraclinical tests in the diagnosis of acute sinusitis in adults and describe what treatments they choose to use. Three hundred GPs were randomly selected. The selection was done in collaboration with the Research Unit for General Practice, University of Aarhus. The questionnaire was sent by mail with one reminder after 4 weeks. Half (149) answered the questionnaire. The study showed that GPs put most emphasis on pain over the sinuses and tenderness over the sinuses. To make the diagnosis they indicated that the most frequent examination were objective ENT examination, palpation of the maxillofacial area and in 75 % of cases the use of CRP near-patient testing. The doctor's diagnostic certainty was found to be 70%. Almost all (90%) prescribed topical vasoconstrictors, in 20 % of cases, topical nasal steroid, and in 70 % of cases were also prescribed penicillin V. The use of local vasoconstrictor is widespread, but the effect of treatment is controversial, as well as treatment with local steroid to counteract oedema of the mucosa of the osteomeatale area. The question of allergy pre disposes to ARS has been debated in several works on the theory that an oedema of the mucosa of the osteomeatale area may lead to obstruction of the sinus ostium, reduce ventilation, leading to mucus retention and thereby increase the risk of bacterial entry of the sinuses. However, there are to date no reliable prospective studies to confirm this hypothesis. Since other work has demonstrated that CRP near-patient testing is a reliable examination to both diagnose and assess the possible prescription of antibiotics, it is surprising that the test is not used more frequently (110-112). I have no explanation for this observation, but assume that the doctors, who do not use the CRP analysis, feel more confident with a diagnosis based on clinical assessment than the doctors who report using CRP analysis. The choice of penicillin V is well chosen also in the light of the Scandinavian tradition. Second most frequently used is macrolides, almost always used as an alternative by suspected penicillin allergy. The group of non-responders did not differ from the responders with regard to practice type or gender. I therefore assume that the management of the disease is similar in the 2 groups so that the risk of selection bias due to the relatively low number of responses are assumed to be small. Finally, they were also asked to indicate the most common reasons why they prescribed antibiotics. 89% answered the question. The major causes were the patient's general condition, disease duration beyond 7 days, the degree of pain and fever. But a number of doctors wrote somewhat surpris-

ingly that they felt a pressure from the patient, and that they had confidence that penicillin could reduce the length of the disease.

Discussion

We primarily chose to concentrate on acute maxillary sinusitis, because we in the planning of the study had determined that maxillary sinus puncture should be included to obtain material for culture and susceptibility testing. But the study also showed that the other sinuses to some extent were involved in the disease after review of the CT. Because of this, I believe, therefore, that the results obtained can be transferred to the diagnosis ARS. During the years 1994 to 2011 many works on acute sinusitis have been published, and in 2005 the first EPOS report (6) was published, it was repeated in 2007 and 2012 (4,8). The aim was to build consensus on the diagnosis and treatment of the disease involving many specialties especially general practice. At the same time it was suggested that the diagnosis of acute sinusitis was changed to acute rhinosinuitis (ARS), since the disease also affects the nasal mucosa. It is also clear that ARS is a differentiated disease that develops gradually, and where all the sinuses are more or less involved, which is also confirmed in this thesis. The probability is that ABRS is preceded by a viral infection, but the specific factors that determine whether a bacterial infection occurs is unknown (54). We had in this study not made consistent CT scans to illustrate the extent to which the other sinuses beyond maxillary sinuses were involved, primarily in the interest of radiation dosage, but upon review of all the CT's we found subsequently that 45% had unilateral changes and 55% had bilateral changes of the maxillary sinuses. In 78 patients the ethmoid cells were also identified on the CT, and of these, 79% had abnormalities. The sphenoid cells were only identified in 21 patients, and of these, 57% had abnormalities. The frontal sinus was not visualized in any of the patients. The disease is frequent and a common problem in general practice. There are no data from Denmark regarding prevalence/incidence. A Norwegian study in 1992-93 from general practice showed that the number of episodes per 1,000 patients per year was 21 (21). Similarly, from the Netherlands in 1987-88 were 21-28 episodes per year per 1,000 patients (7). When the general practitioners have to diagnose they paid most attention to the importance of pain, tenderness and oedema over the sinuses, and maxillary toothache. Purulent nasal discharge plays a minor role. It is in a way unfortunate that the doctors put so much emphasis on pain, because there are many competing causes of facial pain as stated in differential diagnoses. This clinical assessment is not in full agreement with the European position paper on rhinosinusitis and nasal polyps from 2005, 2007 and 2012 (4,6,8). When the ENT doctors diagnose they pay more attention to pus in the cavum nasi than pain (17). One possible explanation is that the patients see the GP's at an early stage of the disease, where purulence is not formed in large quantities, while ENT doctors probably see the patients at a later stage of the disease. Moreover, the ENT doctors have more experience in the clinical examination. Pus is coming down and over the concha inferiors rear edge from the meatus medius, and to visualize the area requires experience in using a rigid or flexible scope. The GP's uses largely the clinical examination to make the diagnosis, while the use of paraclinical examinations are modest, with the exception of measurement of CRP as a near -patient testing after reimbursement was introduced in 1999. I would have expected that the use of CRP analysis over the years would lead to a decrease in antibiotic prescriptions, but it could not be shown in our studies, as opposed to another Danish study (111), that concludes that it cannot be excluded that other factors are involved in the observed reduction of antibiotics. To test the diagnostic value of the various symptoms and signs described in patients with acute maxillary sinusitis, we have used three different reference standards in the clinical study of 174 patients: maxillary sinus puncture, microbiological findings and CT. Patients were examined in the same way by the general practitioners on a standardised chart. Maxillary sinus puncture is the gold standard, as it provides information of the secretion in the maxillary sinus, and by culture, if possible, a microbiological diagnosis. Sinus puncture is not possible in general practice, as it requires specialized knowledge and equipment, and it is unethical to cause the patient the inconvenience, unless it is strictly necessary and in the rare cases the patient should be referred to a specialist. Only 53% of the patients primarily suspected of acute maxillary sinusitis met the diagnostic criteria that were either purulent or mucopurulent antral aspirate. The patient's statement that they had had previously acute maxillary sinusitis was significantly negatively associated to the presence of purulence. This statement further supports that the disease is over diagnosed, and it is easy to repeat this error from time to time. The study showed that in a univariate analysis were unilateral maxillary pain, maxillary toothache and unilateral tenderness with elevated values of CRP and ESR significantly associated with purulence. Compared to EPOS 12 (8) it is only in accordance with unilateral pain and increased ESR/CRP. The definition of EPOS 12 is based on Lindbæk's work (29) where the reference standard is CT, Berg (9) where the reference standard is maxillary sinus puncture and Williams (23) where the reference standard is X-ray. That means that there is one invasive examination and 2 non-invasive. In our study, a multivariate analysis showed, that only elevated levels of CRP and ESR were independently and significantly associated with purulence. 95 % of the patients complain of maxillary sinus pain. Combined maxillary sinus pain with a high value of CRP (> 10 mg/l) and or increased ESR (men > 10 mm/h and women > 20 mm/h) has the clinical criterion a sensitivity of 0.82, specificity 0.57, ppv 0,68 and npv 0.74. Figure1 illustrates the ROC curve for CRP combined with gender adjusted ESR indicated by blue and CRP ROC curve in red. The areas under the curves are, respectively, 0.75 and 0.70. Although the addition of ESR in the clinical criterion increases the area under the curve by 5%, the difference is not significant in relation to CRP alone, and a more clinically useful criterion for the diagnosis of ARS would be only to use CRP. CRP can be read faster, and while the patient is in the clinic, in contrast to the ESR, which can only be read after 1 hour. If the doctor want to be very sure of the diagnosis and thus avoid giving unnecessary antibiotics he must choose a high cut-off value, but in doing so he loses patients with ARS with a lower CRP value in exchange for fewer patients without disease treated unnecessarily with antibiotics. The higher CRP cut-off the higher the sensitivity and corresponding lower specificity and vice versa.

Figure 1.



When CT is used, as reference standard, the analysis shows that 30% of patients primarily suspected of acute maxillary sinusitis have a normal CT. CT is the preferred diagnostic test, also in most scientific studies because it can show even minor pathological changes in the sinuses, compared to X-ray. The limitation of the interpretation is that the examination cannot determine whether retained secretions are purulent or serous. Stratified this material to the severity of changes (mucosal swelling and or fluid level) on a scale from to 6, to either score 5-6 or score below 5, there was a significant correlation with purulent nasal discharge and preceding URTI. There was also a definite correlation between increasing values of CRP and ESR. The patient's statement about previous sinusitis/maxillary sinusitis was again significantly and negatively associated with changes on CT.

When the microbiological diagnosis is used as a reference standard, then the temperature > 38 ºC, maxillary toothache, increased values of CRP and ESR (cut-off values: CRP > 10 mg/l and ESR for men > 10 mm/h and women > 20 mm/h) were found to be significantly associated with the presence of the two most common bacterial species *S. pneumoniae* and *H. influenza* . Virus diagnostics was not carried out. Some respiratory virus could at the time the study was carried out, be grown, but it took a long time and was not routine, and when the study focused on bacterial infection and antibiotic treatment, the virus diagnostics was deselected. None of the traditionally accepted symptoms and signs were particularly sensitive to a specific bacteriological diagnosis. We again found that the patients' own statement on previous sinusitis/maxillary sinusitis, was negatively associated with the growth of either *S. pneumoniae* or *H. influenzae*.

Treatment with vasoconstrictor (adrenergic agents) is widespread. The questionnaire surveys (articles 1 and 7) showed that doctors use this treatment in 90% of the cases, and the consumption has remained largely unchanged over the years. Because the medicine is sold over the counter, the search has been done on www.medstat.dk and it appears that in 2010 were a total of 2.2 million dispensed packages with ACT codes R01AA05, R01AA06 and R01AA07. Since it is sold over the counter, it is not possible from the statistics to determine how much of that is given to children. The purposes of treating locally are to reduce the mucosal oedema and thus improve the sinus ventilation, the drainage from the sinus and improve the air passage in the nose. Experimental studies have shown that the treatment has a pronounced effect on the mucous membrane of the inferior concha and medius, but not on the epithelium of the sinus. Studies also suggest that the treatment has an anti -inflammatory effect, whereas past in vitro studies of the mucociliary clearance, cannot be confirmed in more recent studies that show that there is an improvement in the mucociliary clearance (4). Treatment with topical steroid is based on the allergy predisposes to ARS. However, there are to date no reliable prospective studies to confirm this hypothesis (6). The latter is corresponding to the fact that most patients in our study were enrolled in December, January and February, while the lowest number was found in May and June, and there was not included patients in July (18). The same seasonal trend was found in a Norwegian study from general practice (21).

Antibiotics are prescribed in 50-70 % of cases. There seem to be a slight increase in consumption over the years, despite the introduction of CRP near -patient testing. In the first survey the doctors indicated to use antibiotics in 50 % of cases, whereas it was increased to 70% in the second survey. The randomized treatment study showed that treatment with penicillin V 1333 mg twice daily for 7 days made the patients painless faster than placebo, despite the fact that penicillin V was not prescribed in optimal dosage, which is 1 million IE 3 times daily. The study included 133 patients. The effect is already seen after 3 days of treatment, but only in those patients with the most pain on a scale from 0-5 above 3. After 7 days of treatment, the therapeutic gain = 44 %, as 71 % have recovered completely in the penicillin group versus 37% in the placebo group. From these figures one can calculate that the number needed to treat is 1/0.44 = 2,3.The methodological problems associated with lack of control for compliance and consumption of week analgesics are more fully discussed in the section on bias. The empirical choice of penicillin V as first-line treatment is justified. According to information from the clinical microbiology department in North Jutland, the resistance patterns for the county in 2004 (based on culture results from the primary and the secondary sector) are calculated to: 15% of *H. influenzae* strains are resistant to ampicillin and 3.7% of *S. pneumoniae* strains are resistant to penicillin, which means that at least 75 % (38 % - (38 x 0.15) + 36 % - (36 x 0.037) + 8 %) of the patients, it would be preferable to initiate treatment with penicillin V. Against this is that in our study were all examined *S. pneumoniae* and haemolytic streptococci group A fully sensitive to penicillin, all *H. influenzae* were fully sensitive to ampicillin . With the exception of 1, which was resistant to penicillin *S. aureus*, but full sensitive to meticillin. Among positive cultures with *Moraxella catarrhalis* (n = 4) were 2 examined, showing 1 resistant to penicillin and 1 fully sensitive to penicillin. Only at treatment failure is there an indication for changing therapy to either amoxicillin or if you suspect a beta-lactamase-producing *H. influenzae* to amoxicillin/clavulanate. The study showed that there was a significant effect of penicillin V to a subgroup of patients with acute maxillary sinusitis with strong pain in the maxillary sinuses, which recovered more quickly during penicillin treatment. However, the resistance pattern for *H. influenzae* has changed over the years. The problem is if *H. influenzae* is the dominant flora, then the oral penicillin is not effectively anymore, and you should instead use either amoxicillin or amoxicillin/clavulanate. The reason is that the MIC for penicillin V is too high for the oral dosing to provide sufficiently high concentrations. This thesis, however, shows, that the doctor cannot possible solely on the clinical picture assess which bacterial infection it is.

A Cochrane review from 2008 (91) studied the effect of antibiotic treatment of acute maxillary sinusitis based on 59 separate studies with the following entry criteria: disease duration of 7-30 days and at least 2 of the following symptoms and signs: tenderness of

maxillary sinus, postnasal drip, unilateral facial pain, maxillary toothache and reduced sense of smell, or positive imaging x-ray, ultrasonography, CT, MRI or culture-proven sinusitis, which used many different types of antibiotics (penicillin V, amoxicillin, amoxicillin with clavulanate, cephalosporins, macrolides and tetracycline) concluded that there was moderate evidence that antibiotics for uncomplicated acute sinusitis in general practice and in immunocompetent patients, could reduce the length of the disease marginally. The effect was only found in 6 studies in which antibiotics were compared with placebo, while in the remaining 53 studies where different antibiotics were compared to each other was no difference in the effect of the given antibiotics. It should be noted that a possible explanation for the results is that there are used very different diagnostic criteria in each study.
The relationship between upper and lower airways (United Airways) has been studied in 25 patients with ARS (116). The following parameters were measured at the initial visit at the GP and 8 weeks later: Forced vital capacity (FVC), forced expiratory volume in the first second of a maximal expiratory manoeuvre (FEV1), maximal mid expiratory flow 25-75 % of FVC (F25 -75) and peak expiratory flow (PEF). The study showed a temporary and significant reduction in the lung function rated at F25 -75 and PEF, possibly caused by inflammation of the small airways or through a reflex mechanism that causes an obstruction of the small airways and air trapping. The reason that no changes were detected in the FVC and FEV1 may be that the two parameters are not particularly sensitive to changes in precisely the small airways. The literature contains no information or confirmation of the identified findings in this study.
The final survey (117) summarizes whether the on going debate through the years eventually have had any influence on the management of acute rhinosinusitis in general practice. Doctors still give sinus pain and tenderness highest priority and cough and swollen inflamed turbinates lowest priority. Purulent nasal discharge is still given low priority. The preferred examinations are still the examinations of ear, nose and throat, as well as palpation of the maxilla facial area. In contrast to the first study in which CRP was not available as a near-patient test it now indicated being used in 75% of cases and has out ranked the other examinations as X-ray, pharyngeal swabs and measurement of ESR, which was used in 10% and leukocyte count in 5% of the cases in the study from 1994 (76). Swabs from cavum nasi is not used.
There is a reasonable correlation between specimens taken from the middle meatus under endoscopic control and antral aspiration. According to EPOS12 studies have shown that purulent rhinorrhea with unilateral predominance has a ppv of 50%, and pus in the cavum nasi a ppv of 17% (8).

Conclusion

ARS and especially acute maxillary sinusitis in general practice are over diagnosed because CT detects only changes in 70%, and maxillary sinus puncture shows purulence or mucopurulence in 53% of the patients of whom the doctor suspected of having sinusitis. The usual symptoms and signs are often identical in patients with and without pus in the maxillary sinuses, and the patient's statement that they previously had had the disease is significantly negatively associated with current purulent infection. Pain in the maxillary sinuses occurs in 95% of the patients and is the most frequent symptom that leads the patient to the doctor. Only raised levels of CRP and ESR are independently and significantly associated with pus in the maxillary sinuses.
A clinical criterion defined as: Pain over the maxillary sinuses accompanied by raised value of CRP and/or ESR gives the following diagnostic values: ppv 0.68 and npv 0.74. The ROC curve for CRP combined with gender adjusted ESR compared with the CRP ROC curve shows that the area under the curves is, respectively, 0.75 and 0.70. Although the addition of ESR in the clinical criterion increases the area under the curve, the difference is not significant in relation to CRP alone and a more clinically useful criterion for the diagnosis of ARS will be to use the CRP alone, CRP can be measured in a few minutes while the patient is in the clinic, in contrast to ESR, which takes one hour to read. The disease is most common in younger and 2/3 is women, although we do not know the reason for this gender difference. A temperature of 38 ºC indicates an infection with either *S. pneumoniae* or *H. influenzae*. Patients meeting the clinical criteria and have severe pain (on a scale of 0-5, more than 3) is significantly healthy faster during treatment with penicillin V.
In adults without chronic lung diseases or allergy can be shown a significant association between acute rhinosinusitis and temporary impairment of the lung function (United Airways). This observation has previously only been demonstrated in patients with asthma.

Perspectives

Studies via Audit Project Odense (APO) concerning respiratory tract infections in general practice in 2010 have shown a decreasing use of CRP analyses in the diagnosis of acute sinusitis in two surveys conducted in 2009 and 2010 from 51% to 40%, and in the same period a small increase in the penicillin prescriptions of 7%. The studies are based on 1,868 patient contacts. Choice of antibiotic treatment is not only based on CRP analysis, but other factors may also be involved in this process, as highlighted in this thesis, and it is recommended that in future studies focus on the above matters, just as it should be investigated further how the prescription of antibiotics or no antibiotics influence on patient outcome.
The issue is whether the acute sinusitis is a female disease is unknown. The trend is the same in both general practice and ENT practice. However, since both observations can be attributed to an increased tendency to seek medical/treatment of the problem , one can not on that basis say much about whether women are actually more likely than men to have the disease - let alone why. The challenge is therefore through a prospective cohort study with the aim to reveal the factors that actually determine why we seek doctors and when the ARS is an outcome.
It is well known that URTI can worsen a pre-existing lung disease, when it comes to allergic persons, but that a response has been demonstrated in otherwise lung healthy and not allergic individuals should be followed up with a larger study to elucidate this and possible causes.

Summary

The idea behind this thesis is to present how ARS and especially acute maxillary sinusitis in adults is diagnosed and treated in general practice. The study extends over many years, beginning with the first survey in 1991. Based on doctors' answers, we then investigated the diagnostic values of the symptoms, signs and examinations which the doctors reported using. All patients over 18 years suspected of acute maxillary sinusitis were included consecutively and only once and, after a clinical examination with the GP, they were offered the opportunity to enter into the prospective study referred to acute CT scan and by changes in the CT, immediately referred to sinus puncture**.** Both examinations were conducted at Aalborg Hospital. The disease was found most frequently in younger and 2/3 was women. The reason for this gen-

der difference is unknown. We have assessed the diagnostic values of the symptoms, objective findings and investigations using 3 different reference standards: sinus puncture, microbiological diagnosis and CT scan described in three articles. In all examinations, it appeared that the usual signs and symptoms of acute maxillary sinusitis occur almost equally often and with a few exceptions in patients, with and without pus in the sinus cavities. Pain in the sinus cavities occurring in 95 % of patients, and only elevated levels of CRP and ESR are significantly and independently associated with pus in the sinus cavities. This finding is surprising, because they are two nonspecific markers. CRP tested by near-patient testing has, within the investigations period, been introduced in general practice, and from 1999 the doctors also get reimbursed for performing the test. We have on this background originally defined a clinical criterion with pain over the sinuses accompanied by elevated values of CRP and / or ESR giving a sensitivity of 0.82, specificity 0.57, ppv 0.68 and npv 0.74. But looking at the ROC curve we suggest that a more clinical relevant diagnose will be based on use of CRP alone, as the test can be made easily and fast while the patient is in the clinic compared to the use of ESR.

The disease is over-diagnosed in general practice. In only 53 % of patients, who the GP suspected of having acute sinusitis, was there detected pus or mucopus at the sinus puncture, furthermore the patients' statements that they had had sinusitis was significantly negatively associated with current acute maxillary sinusitis. Almost all patients are prescribed topical treatment to the nose in the form of vasoconstrictor, and between 50 -70 % also antibiotics. The most common bacteria that can be isolated are *S. pneumoniae* and *H. influenzae.* For many years the first drug of choice has been penicillin V, and treatment with penicillin V has followed Scandinavian recommendations. However, the resistance patterns in respect of *H. influenzae* have changed over the years and if the dominant flora is *H. influenzae*, then oral penicillin is not sufficient anymore, and should be replaced by amoxicillin with or without clavulanate. It is reported that the MIC of penicillin V is too high, such that oral dosage cannot provide sufficiently high concentrations. However, in daily clinical practice the doctor does not have the possibility to decide whether the infection is caused by either *S. pneumoniae* or *H. influenzae,* unless a sinus puncture is performed and it is not considered as a standard procedure. The recommended treatment is therefore starting with penicillin V, and at treatment failure switching to amoxicillin with or without clavulanate. It is well known that URTI's can exacerbate a chronic pulmonary disease - like asthma - in allergic patients, but this influence is also demonstrated as described in article 6 where ARS in adults without any sign of chronic lung disease or allergy is accompanied by a temporary reduction lung function. Future research should focus on the use of CRP in general practice, analysing cost-effectiveness of the use of CRP patient outcome in relation to antibiotic treatment, clarification of ARS is a female disease, and a detailed exploration of the relationship between URTI's and impaired lung function in lung-healthy patients.

References

1. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology: A Basic Science for Clinical Medicine. Boston: Little, Brown and Company. 1991.
2. Wulff HR, Gøtzsche PC. Rationel Klinik. Evidensbaserede diagnostiske og terapeutiske beslutninger. København: Munksgaard 2000.
3. Friis H, Bro F, Mabeck CE, Vejlsgaard R. Use of antibiotics in General Practice in Denmark in 1987. Scand J Infect Dis1989;21:551-6.
4. Fokkens WJ, Lund V, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl. 2007(20):1-136.
5. Bretlau P, Brahe-Pedersen C, Ovesen T. Lærebog i Ørenæse og halssygdomme & hoved-halskirurgi. 11 udgave. København: Munksgaard
6. Fokkens WJ, Lund V, Bachert C et al: European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl.2005(18):1-87.
7. Van Duijn NP, Brouwer HJ, Lamberts H. Use of symptoms and signs to diagnose maxillary sinusitis in general practice: comparison with ultrasonography. BMJ 1992;305:684-7.
8. Fokkens WJ, Lund V, Mullol J, Bathert C et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012 Mar;(23):1-298.
9. Berg O, Carenfelt C. Analysis of symptoms and signs in the maxillary sinus empyema. Acta Otolaryngol 1988;105:343-9.
10. Drettner B, Lindholm C-E. The borderline between acute rhinitis and sinusitis. Acta Laryngol 1967;64:508-13.
11. Gwaltney JM. Sinusitis. In: Mandell GL, Douglas RG, Bennett JS. Eds. Principle and Practice of Infectious Diseases, 3rd edition. New York: John Wiley and Sons inc 1990;510-14.
12. Berg O, Carenfelt C. Etiological diagnosis in sinusitis: ultrasonography as clinical complement. Laryngoscope 1985;95:851-3.
13. Axelsson A, Runze U. Symptoms and signs of acute maxillary sinusitis. ORL 1976;38:298-308.
14. Berg O, Bergstedt H, Carenfelt C, Lind MG, Perols O. Discrimination of purulent from nonpurulent maxillary sinusitis. Ann Otol 1981;90:272-5.
15. Engquist S, Lundberg C. Akut sinuit - nær, hur och av vem bør den behandlas? Lækartidningen 1986;83:3112-4.
16. Lindbæk M, Hjortdahl P. Sinusitt i allmenpraksis - behandling og henvisning. Tidsskr Nor Lægeforen 1993;113:478-95.
17. Lindbæk M, Hjortdahl P. Sinusitt i allmenpraksis - en diagnostisk udfordring. Tidsskr Nor Lægeforen 1993;113:700-3.
18. Hansen JG, Schmidt H, Rosborg J, Lund E. Predicting acute maxillary sinusitis in a general practice population. BMJ 1995;311:233-6.
19. Hovelius B, Widæng K. Forkylning eller bihåleinflammasjon? I: Mordh A-A, ed. Infektioner i primærvård. Stockholm: Almquist & Wiksell,1986;75-9.
20. Sande MA, Gwaltney JM. Acute community-acquired bacterial sinusitis: continuing challenges and current management. Clin Infect Dis 2004;39:151-8.
21. Lindbæk M, Hjortdal P, Holth V. Acute sinusitis in adults in Norwegian general practice. Eur J Gen Pract 1997;3:7-11.
22. Lindbæk M, Hjortdal P. The clinical diagnosis of acute purulent sinusitis in general practice – a review. Br J Gen Pract 2002;52:491-5.
23. Williams JW, Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis. Ann Intern Med 1992;117:705-10.

24. Williams JW, David L, Simel DL. Does this patient have sinusitis? JAMA 1993;270:1242-6.
25. Druce HM. Diagnosis of sinusitis in adults: history, physical examination. nasal cytology, echo, and rhinoscope. J Allergy Clin Immunol 1992;90:436-41.
26. Flinn J, Chapmann ME, Wightman AJA, Maran AGD. A prospective analysis of incidental paranasal sinus abnormalities on CT head scans. Clin Otolaryngol 1994;19:287-9.
27. Antila J, Sonninen P, Grenman R. MRI and plain radiographics in acute frontal sinus infections. Rhinology 1993;31:145-9.
28. Unger JM, Schaffer K, Duncavage JA, Milwaukee WI. Computed tomography in nasal and paranasal sinus disease. Laryngoscope 1984;94:1319-24.
29. Lindbæk M, Hjortdahl P, Johnsen UL. Use of symptoms, signs, and blood tests to diagnose acute sinus infection in primary care: comparison with computed tomography. Fam Med 1996; 28:183-8.
30. Lindbæk M, Johnsen UL-H, Kaastad E, Dølvik S, Møll P, Lærum E, Hjortdahl P. CT Findings in General Practice Patients with Suspected Acute Sinusitis. Acta Radiologica 1997;37:708-13.
31. Wittkopf ML, Beddow PA, Russell PT, Duncavage A, Becker SS. Revisiting the interpretation of positive sinus CT findings: A radiological and symptom-based review. Otolaryngol Head Neck Surg 2009;140:306-11.
32. Madani G, Beale TJ. Sinonasal Inflammatory Disease. Semin Ultrasound CT MRI 2009;30:17-24.
33. Hagtved T, Aaløkken TM, Nøtthellen J, Kolbenstvedt A. Røntgen bihuler og lavdose-CT ved akutt sinusitis. Tidsskr Nor Lægeforen 2003:123:3362-4.
34. Kenny TJ, Duncavage J, Bracikowski J, Yildirm A, Murray JJ, Tanner SB. Prospective analysis of sinus symptoms and correlation with paranasal computed tomography scan. Otolaryngol Head Neck Surg 2001;125:40-3.
35. Havas TE, Motbey JA, Gullane PJ. Prevalence of Incidental Abnormalities on Computed Tomographic Scans of Paranasal Sinuses. Arch Otolaryngol Head Neck Surg 1988;114:856-9.
36. Varonen H, Mäkelä M, Savolainen S, Läärä E, Hilden J. Comparison of ultrasound, radiography, and clinical examination in the diagnosis of acute maxillary sinusitis: a systematic review. J Clin Epidemiol 2000;53:940-8.
37. Hansen JG, Lund E. The association between paranasal computed tomography scans and symptoms and signs in a general practice population with acute maxillary sinusitis. APMIS 2011;119:44-8.
38. Kay NJ, Setia RN, Stone J. Relevance of conventional radiography in indicating maxillary antral lavage. Ann Otol Rinol Laryngol 1984;93:37-8.
39. Jannert M, Andreasson L, Holmer NG, Lorins P. A comparison between different ultrasonic display techniques, radiography and invasive control for different disorders of the paranasal sinuses. Acta Otolaryngol 1982; (suppl 389):29-52.
40. Hanson LA, Wadsworth CH. C-reactive protein and its diagnostic usefulness - especially in infections. Med Lab 1980; 8:34-44.
41. Hjortdal P, Landaas S, Urdal P, Steinbakk M. Fuglerud P, Nygaard B. C-reactive protein: a new rapid assay for managing infectious disease in primary health care. Scan J Prim Health Care 1991;9:3-10.
42. Savolainen S, Jousimies-Somer H, Karjalainen J, Ylikoski J. Do simple laboratory tests help in etiologic diagnosis in acute maxillary sinusitis? Acta Otolaryngol (Stockh) 1997;Suppl 529:144-7.
43. Hansen JG, Højbjerg T, Rosborg J. Symptoms and signs in culture-proven acute maxillary sinusitis in a general practice population. APMIS 2009; 117:724-9.
44. Kaliner M. Treatment of sinusitis in the next millennium. Allergy Asthma Proc.1998;19(4):181-4.
45. Savolainen S. Allergy in patients with acute maxillary sinusitis. Allergy 1989; 44(2):116-22.
46. Alho OP, Karttunen TJ, Karttunen R, TuokkoH, Koskela M, Suramo I, et al. Subjects with allergic rhinitis show signs of more severely impaired paranasal sinus functioning during viral colds than nonallergic subjects. Allergy 2003; 58(8):767-71.
47. Hinriksdottir I, Melen I. Allergic rhinitis and upper respiratory tract infections. Acta Otolaryngol Suppl. 1994;515:30-2.
48. Iwens P, Clement PA. Sinusitis in allergic patients. Rhinology 1994;32(2):65-7.
49. Heikkinen T, Järvinen A. The common cold. Lancet. 2003;361 (9351):51-59.
50. Puhakka T, Mäkelä M, Alanen A, Kallio T, Korsoff L, Arstila P, Leinonen M, Pulkkinen M, Suonpää J, Mertsola J, Ruskanen O. Sinusitis in common cold. J Allergy Clin Immunol. 1998;102(3):403-8.
51. Pitkäranta A, Starck M, Savolainen S, Pöyry T, Suomalainen I, Hyypiä T, Carpen O, Vaheri A. Rhinovirus RNA in the maxillary sinus epithelium of adult patients with acute sinusitis. Clin Infect Dis. 2001 Sep 15;33(6):909-11.
52. Evans FO Jr, Sydnor JB, Moore WE, Moore GR, Manwaring JL, Brill AH, Jackson RT, Hanna S, Skaar JS, Holdeman LV, Fitz-Hugh S, Sande MA, Gwaltney JM . Sinusitis of the maxillary antrum. N Engl J Med. 1975 Oct 9; 293(15):735-9.
53. Hamory BH, Sande MA, Sydnor A Jr, Seale DL, Gwaltney JM . Etiology and Antimicrobial Therapy of Acute Maxillary Sinusitis. J Infect Dis. 1979 Feb; 139(2):197-202.
54. Gwaltney JM. Acute Community-Acquired Sinusitis. Clinical Infectious Diseases 1996;23:1209-25.
55. Han JK, Hendley JO, Winther B. Bacterial pathogens of acute sinusitis in the osteomeatal complex during common colds and wellness. Int Forum Allergy Rhinol. 2011 Sep-Oct; 1(5):356-60.
56. Brook I. Sinusitis of odontogennic origin. Otolaryngol Head Neck Surg. 2006;135:349-55.
57. Scheid DC, Hamm RM. Acute Bacterial Rhinosinusitis in Adults: Part 1. Evaluation. Am Fam Physician 2004;70:1685-92.
58. Penttila M, Savolainen S, Kiukaanniemi H, Fosblom B, Jousimies-Somer H. Bacterial findings in acute maxillary sinusitis—European study. Acta Otolaryngol Suppl (Stockholm) 1997;529:165-8.
59. van Cauwenberge PB, Vander Mijnsbrugge AM, Ingels KJAO. The microbiology of acute and chronic sinusitis and otitis media: a review. Eur Arch Otorhinolaryngol 1993;250:3-6.
60. Carenfelt C, Lundberg C, Nord C-E, Wretlin B. Bacteriology of maxillary sinusitis in relation to quality of the retained secretion. Acta Otolaryngol 1978; 86:298-302.

61. van Cauwenberge PB, Verschraegen G, van Renterghem L. Bacteriological findings in sinusitis. Scand J Infect Dis 1976; Suppl 9:72-7.
62. Piccirillo JF. Acute bacterial sinusitis. N Engl J Med 2004;351:902-10.
63. Brook I. Aerobic and anaerobic bacterial flora of normal maxillary sinuses. Laryngoscope 1981;91:372-5.
64. Blomgren K, Hytönen M, Pellinen J, Relander M, Pitkäranta A. Diagnostic accuracy of acute maxillary sinusitis in adults in primary care. Scand J Prim Health Care 2002;20(1):40-4.
65. Joniau S, Vlaminck S, Van Landuyt H, Kuhweide R, Dick C. Microbiology of sinus puncture versus middle meatal aspiration in acute bacterial maxillary sinusitis. Am J Rhinol 2005;19:135-40.
66. Berg O, Carenfelt C, Kronvall G. Bacteriology of maxillary sinusitis in relation to character of inflammation and prior treatment. Scand J Infect Dis 1988; 20:511-16.
67. Klossek J-M, Mesbach K. Presentation and treatment of acute maxillary sinusitis in general practice: A french observational study. Rhinology 2011; 49:84-9.
68. Williams Jr JW, Aguilar C, Mäkelä M, Cornell J, Hollman DR, Chiquette E, Simel DL. Antimicrobial Therapy for Acute Maxillary Sinusitis (Cochrane review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update Software.
69. Moth G, Vedsted P, Olesen F. Kontakt- og sygdomsmønsterundersøgelse KOS 2008. Århus: Forskningsenheden for Almen Praksis. 2010.
70. Incaudo GA. Diagnosis and Treatment of Allergic Rhinitis and Sinusitis During Pregnancy and Lactation. Clinical Reviews in Allergy & Immunology 2004;26:159-77.
71. Marbry RL. Rhinitis of Pregnancy. Southern Medical Journal 1986;79:965-71.
72. obol SE, Frenkiel S, Nachtiga D, Wiener D, Teblum C. Clinical manifestations of sinonasal Pathology during Pregnancy. The Journal of Otolaryngology 2001:30:24-7.
73. Ellegård EK. The Etiology and Management of Pregnancy Rhinitis. Am J Respir Med 2003;286:469-75.
74. Ellegård EK. Clinical and Pathogenetic Characteristics of Pregnancy Rhinitis. Clinical Reviews in Allergy & Immunology 2004;26:149-59.
75. Ellegård EK. Special considerations in treatment of pregnancy rhinitis. Women's Health 2005;1(1):105-14.
76. Hansen JG, Schmidt H. Danske praktiserende lægers diagnosticering og behandling af sinuitis acuta. Ugeskr Læger 1994;156:1934-40.
77. Nørrelund N. Behandling af sinuitis i almen praksis. Ugeskr Læger 1978;140:2792-5.
78. Glad WR. Akutt sinusitt i almen praksis. Tidsskr Nor Lægeforen 1976; 96:1608-9.
79. Young J, de Sutter A, Merenstein D, van Essen GA, Kaiser L, Varonen H, Williamson I, Bucher HC. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. Lancet 2008;371:908-14.
80. Pool MD. Acute bacterial rhinosinusitis: Clinical impact of resistance and susceptibility. Am J Med 2004;117:29-38.
81. Hickner JM, Bartlett JG, Besser RE, Gonzales R, Hoffman JR, Sande MA. Principles of appropriate antibiotic use in acute rhinosinusitis in adults: Background. Ann Intern Med 2001;134:498-505.
82. Blomgren K, Alho O-P, Ertama L, Huovinen P, Korppi M, Mäkelä M, Penttiilä M, Pitkäranta A, Savolainen S, Varonen H, Suonpää J. Acute sinusitis: Finnish clinical practice guidelines. Scan J Inf Dis 2005;37:245-50.
83. Lindbæk M, Hjortdahl P, Johnsen U L-H. Randomised, double blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults. BMJ 1996;313:325-9.
84. Scheid DC, Hamm RM. Acute Bacterial Rhinosinusitis in Adults: Part 2. Treatment. Am Fam Physician 2004;70:1697-704.
85. Ekedahl C. Treatment of maxillary sinusitis. Scan J Infect Dis 1983; (suppl 39): 56-8.
86. Nord CE. Efficacy of penicillin treatment in purulent maxillary sinusitis. A European multicenter trial. Infection 1988;4:209-14.
87. Gwaltney JM, Scheld WM, Sande MA, Sydnor A. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 1992;90:457-61.
88. De Sutter A, Lemiengre M, Van Maele G, van Driel M, De Meyere M, Christiaens T, De Maeseneer J. Predicting Prognosis and Effect of Antibiotic treatment in Rhinosinusitis. Annals of Family Medicine 2006;4:486-93.
89. Hansen JG, Schmidt H, Grinsted P. Randomised, double blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. Scand J Prim Health Care 2000;18:44-7.
90. van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet 1997;349:683-7.
91. Ahovuo-Saloranta A, Rautakorpi UM, Borisenko OV, Liira H, Williams Jr JW
Mäkelä M. Antibiotics for acute maxillary sinusitis. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD000243.
92. Mandal R, Patel N, Ferguson BJ. Role of antibiotics in sinusitis. Curr Opin ect Infect Dis. 2012 Apr; 25(2):183-92.
93. Garbutt JM, Banister C, Spitznagel E, Piccirillo JF. Amoxicillin for Acute Rhinosinusitis. JAMA. 2012;307 (7):685-692.
94. Smith SR, Montgomery LG, Williams JW. Treatment of Mild to Moderate Sinusitis. Arch Intern Med. 2012;172 (6):510-513.
95. Kaiser L, Morabi A, Stalder H, Ricchetti A, Auckenthaler R, Terrier F, Hirchel B, Khaw N, Lacroix J.-S, Lew D. Role of NasopharyngeaL Culture in Antibiotic Prescreption for Patients with Common Cold or Acute Sinusitis. Eur J Clin Microbiol Infect Dis. 2001;20:445-451.
96. Brugman SM, Larsen GL, Henson PM, Honor S, Irvin CG. Increased lower airways responsiveness associated with sinusitis in a rabbit model. Am Rev Respir Dis. 1993;147(2):314-20.
97. Greenberger PA. Therapy in the management of the rhinitis/asthma complex. Allergy Asthma Proc 2003;24(6):403-07.
98. Bachert C, Patou J, Van Cauwenberge P. The role of sinus disease in asthma. Curr Opin Allergy Clin Immunol 2006;6(1):29-36.
99. Kim JS, Rubin BK. Nasal and sinus inflammation in chronic obstructive pulmonary disease. COPD 2007;4(2):163-66.
100. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinus disease with associated reactive airway disease in children. Pediatrics 1984;73:526-9.

101. Osur SL. Viral respiratory infections in association with asthma and sinusitis: a review. Ann Allergy Asthma Immunol 2002;89(6):553-60.
102. Peters E, Scott C, Phillips CD, Wheatley LM, Platts-Mills TAE. Sinusitis and acute asthma in adults. Int Arch Allergy Immunol 1999;118(2-4):372-74.
103. Rossi OVJ, Pirilä T, Laitinen J, Huhti E. Sinus aspirates and radiographic abnormalities in severe attacks of asthma. Int Arch Allergy Immunol 1994;103:209-213.
104. Sugiyama Y. Sinobronchial syndrome. Nippon Rinsho 1999;57:2119-22.
105. Armitage P, Berry G, Matthews JNS. Statistical methods in medical research (3rn ed.). London: Blackwell, 1994.P.127.
106. Miettenen OS. Estimability and estimation in case-referent studies. Am J Epidemiol 1976;103:226-35.
107. Goran MJ, Williamson JW, Gonnella JS. The validity of patient management problems. J Med Educ 1973;48:171-7.
108. Jensen IP, Ejlertsen T. Reappearance of group A streptococci in acute otitis media. Scan J Infect Dis1990;22(4):431-5
109. Ejlertsen T. Branhamella catarrhalis. Prevalence and immunological response in children. Antimicrobial resistance among isolates from children. 1995 Ph.D. Thesis. University of Aarhus. Denmark.
110. Hansen JG, Dahler-Eriksen BS. C-reaktivt protein og infektioner i almen praksis. Oversigtsartikel Ugeskr Læger 2000;162:2457-60.
111. Bjerrum L, Gahrn-Hansen B, Munck AP. C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis. Br J Ge Pract. 2004;54:659-962.
112. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C- reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med. 2010;8:124-33.
113. Young J, Buchner H, Tschudi P, Périat P, Hugenschmidt C, Welge-Lüssen A. The clinical diagnosis of acute bacterial rhinosinusitis in general practice and its therapeutic consequences. J Clin Epidemiol. 2003;56(4):377-84.
114. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P et al. ERS Consensus Statement. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). Eur Respir J. 1995;8(8):1398-1420.
115. Danish Society of Respiratory Medicine. Spirometry – a recommendation (in Danish). Copenhagen: Danish Society of Respiratory Medicine, 1986.
116. Hansen JG. The effect of acute rhinosinusitis on pulmonary function in adults. Prim Care Resp J 2009;18(3):224-5.
117. Hansen JG. Management of acute rhinosinusitis in Danish general practice: a survey. Clin Epidemiol 2011;3:213-6.