Recalcitrant chronic rhinosinusitis. Difficulties in diagnosis and treatment
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Citation for published version (APA):

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SUMMARY

Chapter 1

In the introduction possible functions of the paranasal sinuses, normal sinus anatomy, pathophysiology, CRS disease definition and treatment options are described. The definition of CRS includes the presence of the following symptoms: nasal blockage or nasal discharge, combined with facial pain and/or loss of smell for more than 12 weeks. Endoscopic signs and/or CT scan changes complete the definition. CRS treatment is summarized including treatment with intensive nasal saline irrigation, local corticosteroids, and systemic corticosteroid courses when nasal polyps are predominant. In acute exacerbations of CRS short courses of antibiotics are used. In recalcitrant cases long-term low-dose treatment with antibiotics are prescribed more frequently. When medical treatment is not sufficient, endoscopic sinus surgery is performed to reestablish ventilation and drainage through natural sinus ostia under direct vision. The term recalcitrant CRS is used when conventional treatment is not sufficient, even after repetitive sinus surgery. Relevant background of recalcitrant CRS is described. At the end of this chapter the main aims of this thesis are formulated, enclosing the evaluation of fever as a CRS symptom, the role of osteitis in recalcitrant CRS, the evaluation of long-term low-dose antibiotics as a treatment option as well as local treatment with nebulized antibiotics. In the last part of this thesis radical surgery is assessed as a last resort in a selected group of CRS patients.

Chapter 2

2.1
This chapter reports on a difference in two leading CRS definitions: fever. Patients with CRS, scheduled for surgery were compared with a control group consisting of patients without CRS, suffering from esthetic complaints or obstruction of the nose. Temperature prior to surgery was measured and analysed. In the CRS group the mean temperature was 36.94°C, with a maximum of 37.8°C. The control group revealed a mean temperature of 36.87°C. Analysis demonstrated no significant difference between the mean temperatures of the CRS patients and the controls. Additional analysis, correcting for possible confounders, did not reveal significant differences between both groups either. There have been several attempts to define CRS in the past, but an all including definition or classification system for this disorder does not currently exist. Fever is a factor under discussion. The presented results suggest that fever is not a relevant symptom in CRS.

2.2
The second part of chapter 2 reports on the increasing interest in the underlying bone of the paranasal sinuses as an important player in recalcitrant Chronic Rhinosinusitis. Close inspection of CT scans often reveals areas of increased bone density and irregular thickening of the sinus walls. This osteitic bone could at least partly explain, why inflammation of the mucosa persists. We searched PubMed for all relevant studies and
reviewed the literature. Background, available data, potential diagnostic options, treatment implications, and suggestions for future research are discussed. Osteitis is associated with CRS; however, its role in the pathogenic process is not well defined. More research is needed.

2.3
In the last part of the second chapter our group evaluated the incidence and severity of osteitis in patients with chronic rhinosinusitis using a newly developed and validated Global Osteitis Scoring Scale. We investigated prospectively 102 patients undergoing a computed tomography (CT) sinususes as part of their evaluation for chronic rhinosinusitis and an age- and gendermatched control group of 68 non-rhinosinusitis patients. Seventy-eight of the chronic rhinosinusitis patients completed the nasal subset of the RhinoSinusitis Outcome Measure (RSOM-31) and visual analogue scales. Their CT scans were assessed for osteitis using a newly developed Global Osteitis Scoring Scale. A subsample of 35 scans was additionally scored by a second otorhinolaryngologist and a radiologist. The interrater variability of Global Osteitis Scoring Scale was low. Forty per cent of the chronic rhinosinusitis group and none of the control group had evidence of clinically significant osteitis. In the chronic rhinosinusitis group, the severity of osteitis was correlated with Lund–Mackay score, duration of symptoms and previous surgery, rising in incidence with increasing number of previous operations. There was no association between osteitis and age, gender, smoking, co-existing asthma, allergy or Samter’s triad. Additionally, there was no correlation between osteitis and symptom burden including headache, facial pain and nasal subset score of the RhinoSinusitis Outcome Measure. In patients with recalcitrant chronic rhinosinusitis who have undergone multiple surgeries in the past, the incidence of osteitis can be as high as 64%. It does not seem to be associated with more troublesome symptoms; however, it is strongly associated with previous sinus surgery, which may be a manifestation of a shared endpoint (underlying recalcitrant disease).

Chapter 3

3.1
In the first part of chapter 3 we analysed the outpatient clinic population treated with different long-term low-dose antibiotics at the tertiary referral centre AMC Amsterdam. Eligible patients, who were treated with trimethoprim-sulfamethoxazole or macrolides, were retrospectively identified from the outpatient clinic of the department of otorhinolaryngology in 2009. The 2 main outcome measures were: sinonasal complaints and nasal endoscopic findings. A 5-point grading scale was used to score the results compared with the pre-treatment situation: worse (-1); no change (0); moderate improvement (1); good improvement (2); cured (3). This was measured at several time-points during, and after the antibiotic course, and at the end of the follow-up term. Seventy-six patients with a median age of 49 years were included, 53 per cent had asthma and all of them had undergone sinus surgery. Seventy-eight per cent showed improvement of the symptoms, and 84 per cent demonstrated improvement of the sinonasal mucosa at the end of the course. No significant difference was found between the trimethoprim-sulfamethoxazole and macrolide group. In this investigation long-term low-dose treatment with antibiotics seems to improve CRS symptoms and the appearance of the sinonasal mucosa on nasal endoscopy. However, at this stage, strong conclusions are immature because no placebo-group has
been included. Despite increasing use of long-term low-dose treatment of recalcitrant CRS in referral centres, hard scientific evidence is lacking. More research is urgently required.

3.2
The MACS study is a Randomized Controlled Trial evaluating the efficacy of azithromycin (AZM) in CRS. Patients were treated with AZM or placebo. AZM was given for 3 days at 500 mg during the first week, followed by 500 mg per week for the next 11 weeks. Patients were monitored until 3 months post-therapy. The assessments included Sino-Nasal Outcome Test-22 (SNOT-22), a Patient Response Rating Scale, Visual Analogue Scale (VAS), Short Form-36 (SF-36), rigid nasal endoscopy, Peak Nasal Inspiratory Flow (PNIF), Sniffin’ Sticks smell tests, and endoscopically guided middle meatus cultures. Sixty patients with a median age of 49 years were included. Fifty per cent had asthma and 58% had undergone revision sinus surgery. In the SNOT-22, Patient Response Rating Scale, VAS scores and SF-36, no significant difference between the AZM and the placebo group was demonstrated. Nasal endoscopic findings, PNIF results, smell tests, and microbiology, showed no relevant significant differences between the groups either. At the investigated dose of AZM over 3 months no significant benefit was found over placebo. Possible reasons could be disease severity in the investigated group, under-dosage of AZM, under-powering of the study, the length of the treatment period and the particular macrolide used. More research is required.

3.3
In the last part of chapter 3 we report on the results of a pilot study in order to determine whether nebulized topical antibiotic therapy improves sinusitis symptoms more than saline-based placebo in patients with recalcitrant chronic rhinosinusitis. A randomized, placebo-controlled, double-blind, cross-over pilot study was conducted in 14 patients with recalcitrant CRS. Nasal irrigation with bacitracin/colimycin or placebo using the RhinoFlow nebulizer twice daily was administered in combination with oral levofloxacin. Severity of a diversity of symptoms was measured using the VAS score, a Disease-Specific Symptom Score and the SF-36 questionnaire. Nasal endoscopic findings were also assessed. For most VAS items and Disease-Specific Symptom Scores, a reduction in severity of symptoms was noted in both the bacitracin/colimycin and the placebo group. No significant difference was found between the 2 arms (bacitracin/colimycin or placebo). Most SF-36 items improved, compared with the situation before treatment in both groups. However no significant difference was found between the verum and placebo arm. Endoscopic findings did not reveal significant differences when comparing the 2 treatments. The outcome of this study suggests a beneficial effect of nebulizing the nose with saline. This study again shows that adding antibiotics to local saline is not effective. Although the placebo-controlled studies looking at the effect of local antibiotics are all small they point in the same direction: no effect. Definite conclusions however need a large randomized, multicenter study.

Chapter 4

4.1
Endoscopic Sinus Surgery (ESS) is considered to be the golden standard for surgery in patients with chronic rhinosinusitis and nasal polyposis. However, there is still a small
group of patients unresponsive despite repetitive surgery. Radical surgery aimed at reduction of the inflammatory burden and optimization of drainage of the sinuses has been suggested as a last resort for these patients. A prospective, questionnaire-based study was conducted in a group of 23 patients who underwent Denker’s procedure for refractory chronic rhinosinusitis. Symptoms were evaluated before Denker’s procedure and 12 months and 2 years after surgery. Patients reported improvement of feelings of congestion in 74%, rhinorrhea in 70%, and nasal obstruction in 60% of the cases. The following postoperative improvements were statistically significant: rhinorrhea ($p=0.001$), feelings of congestion ($p=0.02$), and nasal obstruction ($p=0.03$). Reduced olfactory perception and asthma did not improve. Radical surgery may be a viable treatment option in case of recurrent ESS failure.

4.2
Despite effective medical therapy and repetitive endoscopic sinus surgery in the treatment of chronic rhinosinusitis, there still remains a small group of patients without improvement of symptoms. This study evaluates the effect of radical surgery on quality of life and pain in these patients with recalcitrant disease. A prospective, questionnaire-based study was conducted in 23 patients who underwent Denker’s procedure for refractory chronic rhinosinusitis. Quality of life and pain were evaluated before surgery and 12 months and 2 years after surgery with the SF-36 and McGill Pain Questionnaire. Seven of the eight mean scores of the SF-36 postoperatively improved after surgery, with statistical significance for Role Physical ($p=0.048$). Bodily pain showed a strong tendency to significance. Results of the McGill Pain Questionnaire show a significant improvement in most of the subscores after surgery implying less pain. Radical surgery improves the physical burden of chronic rhinosinusitis and pain experience in patients with therapy resistant chronic rhinosinusitis.

Chapter 5
In the final chapter the results of this thesis in general are thoroughly discussed and put into perspective with literature.