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Recalcitrant chronic rhinosinusitis. Difficulties in diagnosis and treatment

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CHAPTER 5

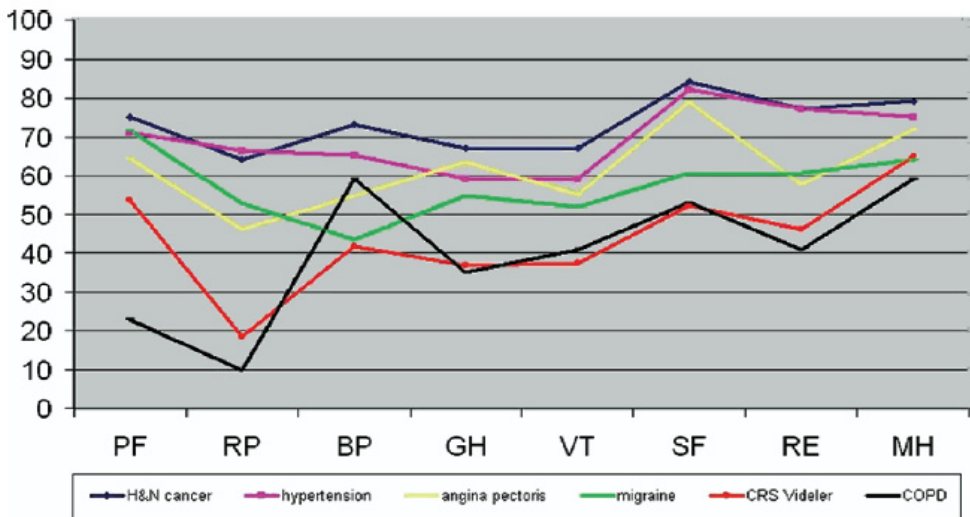
General discussion and conclusions

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BACKGROUND

Chronic Rhinosinusitis is ranked as one of the most prevalent chronic diseases,¹ and significantly contributes to health care expenditure, directly as a result of visits to healthcare practitioners combined with the usage of medical or surgical treatments, and indirectly as a result of loss of productivity and absence from work.¹⁻⁵ CRS is frequently mistaken for a persistent common cold, and because there are no signs outside the patient, acceptance of the disease can sometimes be frustrating. As we have demonstrated in this thesis, quality of life of CRS patients is decreased substantially, and appears to be severe compared with other chronic conditions.^{6,7} When comparing SF-36 results of different diseases published in literature, scores of the recalcitrant CRS population, are even worse than scores measured in patients with head and neck cancer, migraine, and postlingual deaf adult patients (not displayed); the CRS-scores seem to be comparable with patients with COPD (Figure 1).⁷⁻¹⁰

Figure 1. Comparison of SF-36 scores of chronic rhinosinusitis with other diseases. Legends: PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health.



Nowadays, it is well accepted that CRS constitutes a heterogeneous group of diseases with potentially different underlying etiologies. Clinically CRS can be divided into two groups depending on the presence or absence of nasal polyps found on nasal endoscopy. Besides nasal polyps, other factors seem to be relevant, including *Staphylococcus aureus* superantigens,¹¹⁻¹⁵ intracellular microorganisms,^{16,17} fungal infections,¹⁸⁻²¹ biofilm,²² and osteitis of the underlying bone,²³⁻²⁵ among others. These factors could be possible markers for different subgroups of CRS and embody the heterogeneity of the disease. It is likely to

expect that this list of underlying etiologies will lengthen in time when more research in this field will be undertaken.

The multiplicity of possible underlying etiologies makes understanding the pathophysiology of CRS in general, and treatment of the individual patient in daily clinical practice, challenging. Despite the delicate support from evidence of randomized controlled trials, different treatment modalities have been incorporated in guidelines. This lack of evidence based treatment options, combined with the strong tendency of CRS to recur in a vast group of patients, its high and increasing incidence, and the substantial symptom burden of CRS in the individual patient, stimulated us to undertake a number of research projects, attempting to unravel some of the obscurities of recalcitrant CRS. This present thesis is a consequence of these projects, containing 3 main themes. In this discussion chapter we try to put our findings into perspective with the present literature:

- **Etiology and diagnosis, the role of fever and osteitis in recalcitrant CRS**
 - After recognition of differences between the European and the American CRS-definition, we investigated one of them: fever. This was done in a simple but effective prospective evaluation of the body temperature in patients scheduled for sinus surgery compared with a group of patients scheduled to undergo a rhino- or septoplasty.
 - The second part of this chapter reports on one of the factors possibly responsible for the recalcitrant nature of CRS in some patients: osteitis. We performed a literature review on the present knowledge of the role of osteitis in recalcitrant CRS.
 - In addition to the osteitis review, we investigated the incidence and severity of osteitis in patients with CRS using the newly developed Global Osteitis Scoring Scale, as described in part 3.

- **Medical treatment options in recalcitrant chronic rhinosinusitis**
 - Many modes of therapy are used in the battle against recalcitrant CRS in daily clinical practice nowadays. Alongside nasal saline irrigation and corticosteroids, antibiotics in different shapes and administration-modalities embody the cornerstone of CRS therapy. As evidence for the use of antibiotics, both long-term low-dose and topical, is still weak or lacking, we performed a retrospective evaluation on an outpatient clinic population treated with different long-term low-dose antibiotics.
 - In the second part of chapter 3, we report on our randomized, placebo-controlled trial (the MACS study) on the efficacy of long-term low-dose azithromycin in the treatment of recalcitrant CRS.

- In a quest for alternative treatment forms, a randomized controlled pilot study was performed on the efficacy of nebulized bacitracin/colimycin in CRS-patients, which is described in the third part of this chapter.
- **Radical surgery, a last resort?**
 - Despite intensive medical regimes in combination with repetitive endoscopic sinus surgery, there is a small group of patients, who does not improve, but continuously suffers from recalcitrant CRS. In chapter 4 of this thesis we evaluated radical surgery as a possible last resort for a selected group of CRS-patients.

THE ROLE OF FEVER AND OSTEITIS IN RECALCITRANT CRS

Is fever a symptom of CRS?

There are reports that CRS could be a cause of unexplained prolonged fever.^{26,27} Fever is also included in the CRS-definition of the American Academy of Otolaryngology-Head and Neck Surgery.²⁸ However, in the latest European CRS-definition,²⁹ fever is not included as a relevant symptom. The difference in these two leading definitions and the absence of frequent observations of fever in our clinical practice triggered us to evaluate the role of fever as a symptom in CRS. In a prospective study, no significant difference was found between the pre-operative measurements of the body temperature in CRS patients scheduled for endoscopic sinus surgery, compared with a control group planned for surgery of the nose without CRS. When reviewing literature, only very few data on fever in CRS can be found. A prevalence of 3 to 9% in patients undergoing sinus surgery has been reported.^{30,31} In our studied cohort we did not find a temperature higher than 37.8 C in the CRS group. It has already been suggested that the use of fever as a minor symptom in the American definition should perhaps be re-evaluated.³² This simple study puts a finger on a weak spot in CRS research in general, namely the lack of a globally accepted definition, which hampers the comparison of data and the drawing of firm conclusions. Revision of leading definitions, and the formulation of a globally accepted definition should be put on top of the priority list of every CRS research board.

Is osteitis a causative factor in CRS?

Mucosal changes in CRS have been well described. Still a lot has to be learned about the question why this mucosal layer persists to be inflamed. In a group of patients with recalcitrant CRS, bony changes can be observed on CT scans of the paranasal sinuses. In comparison with data on mucosal changes in CRS, limited literature is available on these bony changes. There are studies correlating bony changes seen on CT scan with poorer surgical outcome³³ and with recurrent disease.²³ In our study,³⁴ as well as other reports,^{23,35} the bony changes are related with prior or revision surgery on the paranasal sinuses. We could not demonstrate a relationship between the finding of osteitis of the underlying sinus bone, and disease severity.³⁴ The incidence of the bony changes seen on CT scan varies from 2 to 64%.^{33,36,37} In our study 40% of the CRS group and none of the control group had evidence of osteitis.³⁴ This percentage was 64% in the patients who had undergone revision surgery. Few studies describe a self-developed, unvalidated scale to score bony

changes in patients with CRS.^{33,36,38} Our group developed and validated the Global Osteitis Scoring Scale. This newly developed scale correlated well with the Lund-Mackay score. The Global Osteitis Scoring Scale could be a trigger for future research, and could perhaps be implemented as a tool in future guidelines on CRS.

In our review on the role of osteitis in CRS, data available in literature were interpreted and summarized. Facts worth mentioning are the histological findings in animal as well as human samples, including bone resorption, bone deposition, widening of the haversian system, involvement of the periosteum, fibrosis and cellular infiltrates.^{23,25,36,38-43,45-47} It has been demonstrated that the bony changes, can spread, in the presence of a surgical intervention, not only to the adjacent bone but also to the bone of the opposite sinonasal complex.⁴⁴ Two studies observed widening of the spaces of the haversian system through osteoclastic resorption, followed by increased vascularization during the initial phase of disease. In later stage disease fibrosis of the haversian canals was observed.^{44,46} One could consider these bony changes as signs of infection. However, to date no group was able to demonstrate bacteria in the osteitic bone of the paranasal sinuses. Whether bacteria induce bony remodeling because of associated inflammation or whether they truly infect bone remains unknown. Three possibilities on the role of bacteria have been suggested: 1) bacteria directly destroy the non-cellular components of bone by liberating acid and proteases, 2) bacteria promote cellular processes that stimulate the degradation of bone, or 3) bacteria inhibit the synthesis of bone matrix.⁴⁸

To date there are more questions than answers in the pathophysiologic mechanism of osteitis in CRS. From the available data it is unclear whether osteitis is a responsible factor in recalcitrant CRS, and whether its presence is primarily associated with sinus surgery or should be seen as a more common endpoint of recalcitrant disease. These questions warrant further research.

MEDICAL THERAPY

Should we treat recalcitrant CRS with long-term low-dose macrolides?

The effects of long-term low-dose macrolides seem to extend beyond anti-infectious properties and become apparent with prolonged use at a low dose. Although convincing clinical evidence for the use of long-term low-dose macrolides in the treatment of recalcitrant CRS is lacking, it is incorporated in protocols and guidelines, and is administered to patients at outpatient clinics. In vitro studies are promising, but only few studies have examined the efficacy of long-term low-dose macrolides in CRS in vivo. The majority of the uncontrolled investigations on macrolides have suggested clinical benefit.⁴⁹⁻⁵² In a prospective, randomized controlled trial (RCT) comparing medical and surgical therapy for patients with CRS, prolonged treatment with antibiotics and ESS were equally effective up to one year.⁵³ In the first double-blind, randomized, placebo-controlled trial on the efficacy of 3 months of macrolide treatment in 64 CRS-patients, no significant differences were found. However, a significant benefit of macrolides over placebo was shown in a subpopulation of patients with low IgE.⁵⁴ In a recent RCT on the efficacy of methylprednisolone and a member of another antibiotic family (doxycycline) in 47 patients, a significant effect on nasal polyp size, nasal symptoms, and mucosal and systemic inflammation markers was demonstrated in both treatment arms.⁵⁵ However the effect of

doxycycline was, although longer lasting, very small compared to the effect of prednisolone.

In the first part of chapter 3, we report on the results of a retrospective evaluation of trimethoprim-sulfamethoxazole and macrolides. Symptom reduction as well as improvement of the mucosal condition on nasal endoscopy was achieved equally in both treatment arms. These results are in concordance with the results from Ragab who in a similar group of patients showed an effect of erythromycin comparable with FESS.⁵³

More or less as a counterpart of these data, we report results of the MACS trial in the next part of this chapter. In this second ever RCT on the efficacy of long-term low-dose macrolide treatment, we demonstrated that azithromycin was equally effective as placebo in a group of 60 patients. In contrast with the hopeful findings of supposed immunomodulatory effects of macrolides *in vitro*, convincing clinical benefits have not been demonstrated in the MACS trial or any other placebo-controlled study.

We realize the contradictory findings in chapter 3. In the retrospective evaluation we found that long-term low-dose treatment with both trimethoprim-sulfamethoxazole and macrolides improve the CRS symptom burden and normalize the aspect of the mucosa evaluated by nasal endoscopy. However, in the MACS trial results of the treatment with azithromycin and placebo were equally effective. Although the *in vitro* data of macrolides are promising, and the efficacy in other chronic diseases have been demonstrated,⁵⁶ convincing *in vivo* evidence has not been found to date. It is too simple to say that the results of the double-blind placebo-controlled trial are more valid than the retrospective data. Interestingly the retrospective data show a very significant reduction of symptoms and improvement in endoscopy in both groups of around 80% of the patients. The same is true for the study of Ragab.⁵³ In the double-blind placebo-controlled trial however, only 10/31 of the placebo patients and 14/29 patients on azithromycin improved. So we cannot conclude that the retrospective study shows a placebo effect. Of course the patients and doctors in the retrospective trial knew that the patients received medication, which may deflect the results positively. We cannot disregard the negative results of the double-blind placebo-controlled trial, however we should not totally dismiss long-term macrolides as non-effective at this moment. The difficulty to include patients in these trials with the chance of negative selection (see also further below), the possibility that the groups were too small, the dose too low or the possibility of responders that could not be discriminated because of group size have to be taken into consideration. In daily practice we identify some patients that seem to benefit from long-term low-dose treatment, whereas others fail. Further studies trying to characterize these responders versus non-responders have to be performed. Another point of attention should be the further exploration of possible underlying causes like biofilm, osteitis, superantigens and fungi, being possible targets for future medical treatment. To summarize, the results of the retrospective analysis and the MACS trial did not hold the key for strong recommendations for the use of long-term low-dose macrolides in patients with recalcitrant CRS. However, the findings of this thesis do underscore, the urgent need for more RCT's on this topic. The form of these RCT's and the setting in which they have to be performed needs very careful consideration.

Is topical antibiotic treatment useful?

It is interesting that so few studies have been conducted to explore the therapeutic role of topical nasal antimicrobials, this in contrast with the vast number of papers writing on the intranasal use of topical steroids. Several studies indicate that the local application of antibiotics has a beneficial effect.^{47,57-60} Others have found that nasal saline irrigation is useful, but addition of antibiotics represents no supplementary advantage.⁶¹⁻⁶³ We investigated a group of patients with recalcitrant CRS, selected for the presence of *S. aureus* in the middle meatus culture. In our randomized, placebo-controlled, double-blind, cross-over pilot study, we found that nebulizing the nose and paranasal sinuses had a beneficial effect on several CRS symptoms. However, no additional effect was demonstrated from adding bacitracin/colimycin to the nebulized solution.⁶ Based on the limited amount of literature and this study we cannot recommend the use of local administration of antibiotics in the treatment of recalcitrant CRS. Rinsing has proved again to be important in the reduction of CRS symptoms. More structured, dose-depending investigations, on the efficacy of different intranasal antibiotic solutions, seem warranted.

RADICAL SURGERY, A LAST RESORT?

Is radical surgery an option to treat recalcitrant CRS?

Patients with recalcitrant CRS, form an unfortunate group within the total CRS population. CRS-symptoms persist, despite a series of ESS procedures in combination with maximum peri-operative medical management. The functional approach has proven to be insufficient to break the vicious cycle of recalcitrant CRS in this group. Radical surgery could be an option, aimed at reduction of the inflammatory burden and optimization of drainage and aeration of the sinuses in patients with CRS. In contrast with literature on radical sinus surgery on for example inverted papilloma, angiofibromas, mucocoeles and sinonasal malignancies, reports on the role of radical surgery in treatment of recalcitrant CRS is limited to only a couple of reports. In these studies, radical surgery (medial maxillectomy, (modified) Denker's procedure) has been retrospectively evaluated, and authors conclude that it is a safe and effective last resort for a selected group of patients. Improvement of nasal obstruction, headache, feeling of fullness, postnasal drip, rhinorrhea, and facial pain have been reported.⁶⁴⁻⁶⁶

We performed a prospective evaluation on a group of 23 patients suffering from recalcitrant CRS who were unresponsive to conventional treatment. As a last resort to treat their complaints they all underwent radical surgery. A self-developed list of disease specific questions, the McGill pain questionnaire and the Short Form-36 were performed before and several times postoperatively, up till 2 years. Patients reported significant improvement of feelings of congestion in 74%, rhinorrhea in 70%, and nasal obstruction in 60% of the cases. This improvement was sustainable up till 2 years post surgery. Reduced olfactory perception and asthma did not improve.⁶⁷ The calculated postoperative scores of the McGill Pain questionnaire were compared with the preoperative situation. Results showed a lower score after surgery compared with the preoperative score in all the subscores, implying less pain.⁷ As mentioned earlier at the start of this discussion chapter, the SF-36 scores of the CRS population and thus the impact on QoL of the disease were mostly comparable with the symptom burden of chronic obstructive pulmonary disease and can be classified as severe in comparison with other chronic disorders. These findings match

with other published data and allow us to put the symptom burden of CRS/NP in perspective.⁶⁸ The outcome of the SF-36 showed improvement after surgery in 7 of the 8 domains. After statistical analysis improvement in role physical appeared to be significant 2 years after radical surgery. This should be interpreted that patients have less impairment in work or other daily activities as a result of physical health problems. Revision surgery was not indicated for any of our patients within 2 years after surgery. Our prospective data suggest that radical surgery may be a viable treatment option to achieve symptom reduction after repetitive ESS failure. It improves the physical burden of chronic rhinosinusitis and pain experience in patients with therapy resistant chronic rhinosinusitis.

There is still debate whether radical surgery of the maxillary sinus is a feasible last treatment option in cases of therapy resistant chronic rhinosinusitis of the maxillary sinus to achieve improvement of quality of life and reduction of symptoms. This discussion is in contrast with chronic frontal sinusitis, where radical surgery according to Draf (Draf III procedure) already has been accepted as an effective last therapeutic option to improve frontal drainage and relieve disabling frontal headache.^{69,70} There is little literature on the impact on quality of life of Draf III procedure. Schulze et al.⁷¹ reported improved symptoms and decreased medication requirements in the majority of patients. Recently, there has been a trend in research on chronic rhinosinusitis, to fill in the gaps between all the objective assessments of CRS with subjective outcome measures like general quality of life measures and disease specific questionnaires.

WHAT IS THE VALUE OF THE FOUND DATA?

Now it is time to look back

In this thesis we attempted to answer some questions on recalcitrant CRS. The answers originated from the data gathered and analysed in different projects. In this final chapter we have tried to put our findings in perspective with recent literature. But there seems to be more. What were important hurdles on the way to reach our data? What is the value of the found results and formulated conclusions? Here we reflect on a number of these questions and describe some problems we faced along the way.

We experienced that the enrolment of adequate numbers of suitable CRS patients in the projects, was a returning challenge. Although patients from all over the Netherlands suffering from recalcitrant CRS, are referred to the Academic Medical Centre Amsterdam, distilling representative groups of patients, suitable to enrol into trials, appeared extremely hard. Common argumentation of patients was the fact that they did not want to risk a placebo treatment. Some of them told us that they liked the current treatment and did not want to change. Others addressed to the remark that they disliked the idea of randomization. These conceptions were hard to adjust. Moreover it is difficult to envision whether the patients that do agree to participate in a trial are a random selection of the patients we see in clinical practice. When setting up a trial, the formulation of inclusion and exclusion criteria always is one of the first things that have to be done, in order to create a homogeneous study population. But is a studied group based on these criteria representative for the general population faced at the outpatient clinic,⁷² or do we study a particular subpopulation? Can we translate conclusions made on the results of clinical trials, directly to guidelines and treatment strategies? In some papers on this topic it has

been stated that the elderly subpopulation for example, has been chronically underrepresented in research on cancer.⁷³⁻⁷⁵ When realizing this, it is not difficult to foresee the possibility that, in the ageing population of the western world, the comparability of study samples with the general population might decrease in time. Another example of a factor facing similar problems is concomitant disease. In many projects, including ours, some concomitant diseases are out-filtered by exclusion criteria, which is impossible at the outpatient clinic population. Of course there are more, mostly vulnerable, subgroups and minorities less studied. A number of papers have recently pointed to the problems of nonrepresentative patients (and settings) in trials.^{72,76-79} To conclude, every clinical trial represents a compromise between a homogeneous, clearly defined study sample and a heterogeneous group representing the overall population with the respective disease. This let us to conclude that RCT's but not perse double-blind placebo-controlled RCT's should be done, to allow a larger number of patients to be evaluated. Careful evaluation of responders and nonresponders in these groups hopefully will lead us to better understanding of subpopulations that can be treated effectively.

A problem with a totally different background was the problem to raise funds for CRS research. It appeared a great challenge, and in most cases impossible, to raise funding to perform research. This became clear during the set up and performance of the MACS trial. Although randomized medication was kindly provided by the inventors of the used antibiotic, no other support could be found for this only second ever RCT on the efficacy of macrolides in the treatment of CRS. The MACS trial was eventually performed by a group of European rhinologists who combined forces and took up the gauntlet. We could say that it seems that research on recalcitrant CRS is neglected and sent of to the background when funds are available and divided. This contrasts the (rising) incidence of CRS of 10% in Europe, the demonstrated severe symptom burden and back force on quality of life, and the substantial health care expenditure of around 68 million euros in the Netherlands alone.

The section on medical treatment in CRS demonstrates negative results in the MACS trial, as well as in the pilot-cross over study on the efficacy of nebulized bacitracin/colimycin. It has been suggested that clinical trials with negative results are less likely to be published, and if they do take twice as long,⁸⁰⁻⁸² which in some cases was experienced first hand when submitting articles to scientific journals. Positive results, above all when supported by the pharmaceutical industry, do better when publishing is concerned. This could be considered as a great source of bias in scientific literature in general.

It is not intended here to present a complete list of comments on research versus clinical practice. Both fields need each other. Many clinicians base their treatment choices relying on trial outcomes to formulate clinical decisions regarding individual patients. In this clinical decision-making process, evidence-based medicine may play a significant role by collecting and evaluating the best available evidence. Randomized controlled trials, and meta-analyses of RCT's, are considered to provide evidence of the highest grade. In some cases it could be wise to combine the results of a RCT with a post-RCT observational study to compensate for the hiates of the RCT before newly developed treatment regimes are implemented in widely used advises. For now, there seem to be enough hypothesis-generating studies, both clinical and basic. The time has come for adequately powered blinded randomized trials in the treatment of CRS. Future research will focus on better

GENERAL DISCUSSION AND CONCLUSIONS

classification of chronic rhinosinusitis and tailoring therapy according to different cellular inflammatory characteristics. Commonly used medications need to be studied in randomized controlled trials to determine their place in current therapy. At least one more randomized controlled trial on macrolide therapy is highly desirable.

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CHAPTER 5

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