Recalcitrant chronic rhinosinusitis. Difficulties in diagnosis and treatment

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Long-term low-dose antibiotics in recalcitrant chronic rhinosinusitis: a retrospective analysis

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Submitted to Rhinology for publication
CHAPTER 3.1

ABSTRACT

Introduction
In recalcitrant Chronic RhinoSinusitis (CRS) treatment with intranasal corticosteroids, short-term antibiotics and even sinus surgery is frequently insufficient. Long-term low-dose administration of antibiotics has been suggested as a treatment option in these patients. We analysed the outpatient clinic population treated with different long-term low-dose antibiotics at the tertiary referral centre AMC Amsterdam.

Patients and methods
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.

Results
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.

Discussion
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 clinical evidence is lacking. More research is urgently required.
INTRODUCTION

In the last decades, the management of Chronic RhinoSinusitis (CRS) has improved substantially. According to the EP3OS-management-schemes, patients with CRS are primarily treated with nasal saline irrigation, intranasal corticosteroids, and in more severe cases with antibiotics and/or systemic steroids. In patients who do not optimally respond to this strategy, Endoscopic Sinus Surgery (ESS) is performed. Because CRS could be considered as a chronic mucosal disease, in some cases with participation of the underlying bone or biofilm, long-term low-dose antibiotics are administered more frequently in tertiary referral centres. However, evidence for this treatment regime in literature is limited and weak.

The department of Otorhinolaryngology at the Academic Medical Centre AMC Amsterdam is a tertiary care centre for patients with CRS. All the patients referred have already been treated with medical therapy, and a vast majority of them already have undergone ESS. After careful evaluation with rigid nasal endoscopy, CT scan of the paranasal sinuses, laboratory investigation, allergy testing, smell testing and culturing, an optimal management regime is started including intensive nasal saline irrigation (with or without baby shampoo), intranasal corticosteroids, antibiotics, systemic corticosteroids and if needed a number of more tailored medical treatments with less scientific proof like local antibiotics, leucotrienes antagonists, anti-IgE, and trial drugs. If this treatment is insufficient, patients with recalcitrant CRS are given the choice to either have long-term low-dose antibiotic treatment or revision surgery. This revision sinus surgery again is embedded in maximal medical therapy. When patients choose to start with long-term antibiotic treatment, in most of the cases we start with an arbitrarily chosen 3 months treatment period, which is prolonged when proven effective. A substantial group appears to respond to this regime in both symptom reduction and improvement of the sinus mucosa evaluated with rigid nasal endoscopy. The long-term low-dose treatment is ended when patients are in a stable situation for some time, this can be after many months of treatment. Liver and renal functions are monitored every 6 weeks. If this regime still is insufficient, as a final resort medial maxillectomy ((endonasal) Denker’s procedure) and/or extensive frontal surgery (Draf III) is performed. A life-long nasal rinsing regime is an inevitable consequence of this type of radical surgery.

Although the pathophysiology of CRS is poorly understood, it is considered a mucosal disease with many different phenotypes. External factors like bacteria, fungi and viruses can initiate the chronic infection. However, the host response can vary, and the same stimuli can give different results in different patients. This reaction in severe cases eventually leads to mucosal swelling, increased number of seromucous glands, remodeling of the ciliated epithelium, combined with an infiltration with inflammatory cells, possibly leading to a vicious cycle. The infectious etiology in combination with the constant inflammation could justify the use of long-term low-dose antibiotics with antimicrobial as well as immunomodulatory properties.

At our centre, most prescribed antibiotics for this purpose are trimethoprim-sulfamethoxazole and macrolide antibiotics, mostly azithromycin and clarithromycin. We found no literature on the prolonged treatment with trimethoprim-sulfamethoxazole in CRS. In research most attention, especially in vitro, was put to the antibiotics of the macrolide
family. Besides their antimicrobial effects, the mechanism of macrolides is thought to be anti-inflammatory, based on the blockage of the production of pro-inflammatory cytokines, such as interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α), combined with effects on neutrophil migration and adhesion, and modulation of synthesis and secretions of mucus.\textsuperscript{14-15} Both trimethoprim-sulfamethoxazole and macrolides have proven to be prescribed safely for a prolonged time. Trimethoprim-sulfamethoxazole is widely used for long-term prophylaxis and treatment of infections of the urinary and respiratory tracts.\textsuperscript{16-18} Low-dose long-term macrolides also proved to be safe and have been investigated in a small number of studies. The majority of the uncontrolled investigations evaluated macrolides using varying outcome measures, and have suggested clinical benefit.\textsuperscript{19-22} In a prospective, randomized controlled trial comparing medical and surgical therapy for patients with CRS, the authors have demonstrated that prolonged treatment with antibiotics and FESS were equally effective up to one year.\textsuperscript{23} In the first performed, double-blind, randomized, placebo-controlled trial on the efficacy of 3 months 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. In this group, Sino-Nasal Outcome Test-20 (SNOT-20), nasal endoscopy, saccharine transit time, and IL-8 levels in nasal lavage fluid improved in the antibiotic arm compared with placebo.\textsuperscript{24}

In an attempt to further evaluate the efficacy of long-term low-dose antibiotics as an alternative treatment option for recalcitrant CRS, we retrospectively analysed the outpatient clinic population treated with prolonged antibiotics at our tertiary care centre.

PATIENTS AND METHODS

Patients
All patients met the EP\textsuperscript{3}OS criteria for CRS,\textsuperscript{25} and all had a history of extensive medical treatment and sinus surgery. Patients did not use an antibiotic course within 1 month, nor did they undergo sinus surgery within 3 months before start of the evaluated long-term low-dose antibiotic course. Exclusion criteria for this retrospective evaluation were: massive nasal polyposis (grade 2 and 3), impairment of liver or renal function, cystic fibrosis, immune deficiency needing intravenous immunoglobulins, and systemic diseases affecting the nose and paranasal sinuses (e.g., Wegener’s granulomatosis or sarcoidosis). Most patients used nasal saline irrigation daily. Intranasal or pulmonary steroids were allowed, under the restriction that the dosage did not increase twice or more, during the evaluated antibiotic course.

Long-term low-dose antibiotic therapy
Two different families of orally administered long-term low-dose antibiotics were evaluated in this study. Trimethoprim-sulfamethoxazole was prescribed in a dosage of 960 mg twice daily during 2 weeks, followed by 960 mg/day in the next weeks of treatment. A second cohort of patients was treated with macrolides of which azithromycin was administered in most cases, in a dosage of 500 mg daily which was in some cases reduced to every other day, twice a week or even once a week depending on the clinical picture. Azithromycin has pharmacokinetic properties, which allow, even after a single dose once weekly, persistently elevated concentrations in tissue.\textsuperscript{26-29} In 5 cases, clarithromycin, another member of the
macrolide family, was prescribed in a dosage of 250 mg twice daily in the first 2 weeks, prolonged with 250 mg/day.

Study design
Eligible patients were retrospectively identified from the outpatient clinic of the department of otorhinolaryngology in 2009. Corresponding records were collected and studied by at least 2 of the authors independently. Collaborating members of a team of rhinologists performed all recorded examinations during outpatient visits. The 2 main outcome measures were: sinonasal complaints and nasal endoscopic findings. A 5-point grading scale was used to score the results compared to the pre-treatment situation: worse (-1); no change (0); moderate improvement (1); good improvement (2); cured (3). The main time-points assessed were: after 6 and 12 weeks and after 6, 12, and 24 months. Extra time points included: at the end of the course, and at the end of the follow-up term. We also have divided the group in responders and non-responders. Responders were the patients who showed moderate to good improvement, or reported they were cured (score 1 to 3). Non-responders showed no improvement or got worse (score -1 and 0). Evaluation was terminated in most cases when no more data were available, mainly because of lost to follow-up, while patients with satisfying results were sent back to their referral doctors. Other end-points were: substantial medical intervention, or new sinus surgical procedure.

Statistical analysis
All data were entered into a computerized database and analysis was conducted using statistical software package SPSS version 16.0 statistical software, after consulting a medical statistician. Wilcoxon signed ranks tests were performed to evaluate the effect of antibiotic treatment on different time-points. Mann Whitney U tests, Kaplan Meier curves and Log Rank tests were used to assess statistical differences between the 2 different antibiotic groups. The Fischer exact test was used to compare patient characteristics between responders (moderate improvement, good improvement or cured) and non-responders (worse or no change).

RESULTS
Patient characteristics
Of the 104 patients identified at the outpatient clinic, 28 patients met one of the exclusion criteria or documentation was insufficient. Seventy-six patients were included and evaluated. In all patients conventional medical treatment as described above did not substantially relief symptoms. All of them underwent sinus surgery, with a median of almost 3 procedures. As a result of the retrospective set up of this analysis the length of the course of antibiotics was variable, with a minimum of 79 days. The mean follow-up time after stop of the antibiotic administration for the total group was 4.7 months (trimethoprim-sulfamethoxazole: 4.9 months, macrolides: 4.4 months). Complete patient characteristics are displayed in Table 1.
| Table 1. Patient characteristics  
TSM: trimethoprim-sulfamethoxazole; MAC: macrolides |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>TSM</td>
</tr>
<tr>
<td>Patients</td>
<td>76</td>
<td>43</td>
</tr>
<tr>
<td>Male : female</td>
<td>38:38</td>
<td>20:23</td>
</tr>
<tr>
<td>Median age</td>
<td>47 year (range, 12-70)</td>
<td>46</td>
</tr>
<tr>
<td>Sinonasal complaints (median)</td>
<td>10.9 year (range, 1-40)</td>
<td>10.3</td>
</tr>
<tr>
<td>Number of previous procedures (median)</td>
<td>2.9 (range, 1-14)</td>
<td>2.9</td>
</tr>
<tr>
<td>Allergy</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Asthma</td>
<td>53%</td>
<td>49%</td>
</tr>
<tr>
<td>Mild nasal polyposis</td>
<td>65%</td>
<td>67%</td>
</tr>
<tr>
<td>ASA</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Active smoker</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Previous surgery:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infundibulotomy</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ethmoidectomy</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Sphenoidectomy</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Frontal surgery</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Polypectomy</td>
<td>36%</td>
<td>37%</td>
</tr>
<tr>
<td>Claoué</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>Caldwell-Luc</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Denker</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Draf III</td>
<td>13%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Duration of course
The mean length of the trimethoprim-sulfamethoxazole course was 232 days (range, 81-802). For the macrolides this was 189 days (range, 79-601). Responders who's sinonasal symptoms improved did have a mean antibiotic course of 232 days. In the group of non-responders, the mean length of the course was 150 days. Patients whose endoscopic findings responded well used a long-term low-dose course of 223 days. In the non-responding group this was 166 days.

Efficacy of long-term low-dose antibiotics
Symptoms and nasal endoscopic findings were scored after 6 and 12 weeks and after 6, 12, and 24 months. Because there were too many missing data on 6 weeks, and 12 and 24 months, results could not be reported. We decided to focus on 2 other main time-points: the cessation of the antibiotic course and the end of follow-up.

In the total group, sinonasal symptoms responded well (moderate improvement to cure, score 1 to 3) in 59 patients (78%). After a mean follow-up of 4.7 months after cessation of the antibiotic course, still 52 patients (68%) were present in this well-responding group. The nasal endoscopic findings showed similar results. During the antibiotic course, nasal endoscopy in the total group showed response (moderate improvement to cure) in 64 patients (84%). After cessation of the antibiotic course and the mean follow-up of 4.7 months, 58 (76%) patients were recorded to have an improvement of the nasal mucosa on endoscopy. Although the results at the end of follow-up for both symptoms and endoscopy were still satisfactory, the decrease in score over time was statistically significant (symptoms p=0.003, endoscopy p=0.001). All the percentages and results are shown in Table 2.
Table 2. Results during the use of antibiotics versus results at the end of follow-up.

<table>
<thead>
<tr>
<th>symptoms</th>
<th>during antibiotics n=76</th>
<th>end of follow-up n=76</th>
<th>test for change in time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1 worse</td>
<td>1.3%</td>
<td>1.3%</td>
<td>p= 0.003</td>
</tr>
<tr>
<td>0 no change</td>
<td>21.1%</td>
<td>30.3%</td>
<td></td>
</tr>
<tr>
<td>1 moderate improvement</td>
<td>36.8%</td>
<td>39.5%</td>
<td></td>
</tr>
<tr>
<td>2 good improvement</td>
<td>31.6%</td>
<td>22.4%</td>
<td></td>
</tr>
<tr>
<td>3 cured</td>
<td>9.2%</td>
<td>6.6%</td>
<td></td>
</tr>
<tr>
<td>mean score</td>
<td>1.3</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>median score (IQR)</td>
<td>1 (1-2)</td>
<td>1 (0-2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>endoscopic findings</th>
<th>during antibiotics n=76</th>
<th>end of follow-up n=76</th>
<th>test for change in time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1 worse</td>
<td>1.3%</td>
<td>1.3%</td>
<td>p= 0.001</td>
</tr>
<tr>
<td>0 no change</td>
<td>14.5%</td>
<td>22.4%</td>
<td></td>
</tr>
<tr>
<td>1 moderate improvement</td>
<td>38.2%</td>
<td>43.4%</td>
<td></td>
</tr>
<tr>
<td>2 good improvement</td>
<td>31.6%</td>
<td>22.4%</td>
<td></td>
</tr>
<tr>
<td>3 cured</td>
<td>14.5%</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>mean score</td>
<td>1.5</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>median score (IQR)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td></td>
</tr>
</tbody>
</table>

*Wilcoxon signed ranks test

At the end of the antibiotic course 5 patients responded well on endoscopy, but were scored as non-responder at the symptom score. At the end of follow-up 6 patients were responder on endoscopy but were non-responders on the symptom score. No patients scored better on the symptom score than on nasal endoscopy.
Trimethoprim-sulfamethoxazole versus macrolides

Sinonasal symptoms responded well (moderate improvement to cure) in 34 patients (79%) treated with long-term low-dose trimethoprim-sulfamethoxazole. At the end of a follow-up of 4.9 months this was decreased to 70% of the patients. Five patients (12%) were symptom free at the end of the course and 4 (9%) at the end of follow-up. Sinonasal symptoms of patients treated with macrolides responded well in 25 patients (76%) at the end of treatment. At the end of a mean follow-up of 4.4 months, this was decreased to 67%. During the course 2 patients (6%) reported they were symptom-free. After the stop of the course, mild symptoms recurred in one of them.

The nasal endoscopic findings improved (moderate improvement to cure) in 36 patients (84%) at the end of the trimethoprim-sulfamethoxazole treatment period, which decreased to 72% at the end of follow-up. Nasal endoscopic findings were graded as cured in 6 patients (14%) during the course, which decreased to 5 (12%) after stop of the treatment. In the macrolide cohort, nasal endoscopic findings responded well in 28 patients (85%). At the end of follow-up a limited back-fall was found to 82%. Nasal endoscopic findings were graded as cured in 5 patients (15%) during the course, which decreased to 3 patients (9%) at the end of follow-up.

We compared the scores of trimethoprim-sulfamethoxazole with the macrolides results. In this studied population, no significant differences were found between trimethoprim-sulfamethoxazole and macrolides neither in de symptoms, nor in nasal endoscopic findings (Table 3). We reassessed the data comparing the trimethoprim-sulfamethoxazole patients to the azithromycin group by leaving the clarithromycin patients out. No substantial differences were found in the datasets with or without clarithromycin. An additional analysis was performed with Kaplan Meier curves. The total percentage of responders in time for both trimethoprim-sulfamethoxazole and macrolides were displayed and analysed with a Log Rank test. Again no significant difference was found between the 2 antibiotic groups (see the symptom and endoscopy Kaplan Meier curve, in Figure 1 and 2 respectively).
Table 3. Trimethoprim-sulfamethoxazole versus macrolides.

<table>
<thead>
<tr>
<th>symptoms during antibiotics</th>
<th>trimethoprim-sulfamethoxazole n=43</th>
<th>macrolides n=33</th>
<th>test for difference between antibiotics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1 worse</td>
<td>0%</td>
<td>3%</td>
<td>p=0.609</td>
</tr>
<tr>
<td>0 no change</td>
<td>20.9%</td>
<td>21.2%</td>
<td></td>
</tr>
<tr>
<td>1 moderate improvement</td>
<td>37.2%</td>
<td>36.4%</td>
<td></td>
</tr>
<tr>
<td>2 good improvement</td>
<td>30.2%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>3 cured</td>
<td>11.6%</td>
<td>6.1%</td>
<td></td>
</tr>
<tr>
<td>mean score</td>
<td>1.3</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>median score (IQR)</td>
<td>1 (1-2)</td>
<td>1 (0.5-2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>symptoms at end of follow-up</th>
<th>trimethoprim-sulfamethoxazole n=43</th>
<th>macrolides n=33</th>
<th>test for difference between antibiotics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1 worse</td>
<td>0%</td>
<td>3%</td>
<td>p=0.804</td>
</tr>
<tr>
<td>0 no change</td>
<td>30.2%</td>
<td>30.3%</td>
<td></td>
</tr>
<tr>
<td>1 moderate improvement</td>
<td>46.5%</td>
<td>30.3%</td>
<td></td>
</tr>
<tr>
<td>2 good improvement</td>
<td>14%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>3 cured</td>
<td>9.3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>mean score</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>median score (IQR)</td>
<td>1 (0-1)</td>
<td>1 (0-2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>endoscopy during antibiotics</th>
<th>trimethoprim-sulfamethoxazole n=43</th>
<th>macrolides n=33</th>
<th>test for difference between antibiotics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1 worse</td>
<td>0%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>
### Long-term Low-dose Antibiotics in Recalcitrant Chronic Rhinosinusitis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trimethoprim-sulfamethoxazole (n=43)</th>
<th>Macrolides (n=33)</th>
<th><strong>p</strong> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no change</td>
<td>16.3%</td>
<td>12.1%</td>
<td><strong>p=0.996</strong></td>
</tr>
<tr>
<td>1 moderate improvement</td>
<td>37.2%</td>
<td>39.4%</td>
<td></td>
</tr>
<tr>
<td>2 good improvement</td>
<td>32.6%</td>
<td>30.3%</td>
<td></td>
</tr>
<tr>
<td>3 cured</td>
<td>14%</td>
<td>15.2%</td>
<td></td>
</tr>
<tr>
<td><strong>mean score</strong></td>
<td>1.4</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td><strong>median score (IQR)</strong></td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td></td>
</tr>
</tbody>
</table>

*Endoscopy at the end of follow-up*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trimethoprim-sulfamethoxazole (n=43)</th>
<th>Macrolides (n=33)</th>
<th><strong>p</strong> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no change</td>
<td>27.9%</td>
<td>15.2%</td>
<td><strong>p=0.330</strong></td>
</tr>
<tr>
<td>1 moderate improvement</td>
<td>44.2%</td>
<td>42.4%</td>
<td></td>
</tr>
<tr>
<td>2 good improvement</td>
<td>16.3%</td>
<td>30.3%</td>
<td></td>
</tr>
<tr>
<td>3 cured</td>
<td>11.6%</td>
<td>9.1%</td>
<td></td>
</tr>
<tr>
<td><strong>mean score</strong></td>
<td>1.1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td><strong>median score (IQR)</strong></td>
<td>1 (0-2)</td>
<td>1 (1-2)</td>
<td></td>
</tr>
</tbody>
</table>

*Mann Whitney U test*
CHAPTER 3.1

Figure 1. Total responders in time for symptoms.

Grey line: TSM
Dotted line: MAC
P=0.399

Figure 2. Total responders in time for endoscopic findings.

Grey line: TSM
Dotted line: MAC
P=0.867
LONG-TERM LOW-DOSE ANTIBIOTICS IN RECALCITRANT CHRONIC RHINOSINUSITIS

Five patients in the macrolide group and 7 patients in the trimethoprim-sulfamethoxazole group used a short course of systemic corticosteroids at the start of the antibiotics. Closer inspection did not reveal a substantial better score than patients without an additional corticosteroid course at the start, although numbers are too small to draw definite conclusions. In a small group of patients, 3 in both groups, there was lack of signs of improvement. Therefore they were scheduled for sinus surgery and follow-up was terminated.

Subgroup analysis
In an attempt to find patient characteristics with prognostic value, we evaluated the occurrence of mild nasal polyps, allergy, asthma, ASA-triad, and smoking. In the symptom, as well as the nasal endoscopy data, none of the patient characteristics were significantly different when comparing the responding and non-responding group, but the numbers were small. Percentages and results of the Fischer exact test are shown in Table 4.

Table 4. Responders versus non-responders.

<table>
<thead>
<tr>
<th>symptoms</th>
<th>responders n=59</th>
<th>non-responders n=17</th>
<th>p-value Fischer exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>allergy</td>
<td>25 (42%)</td>
<td>5 (29%)</td>
<td>0.41</td>
</tr>
<tr>
<td>asthma</td>
<td>32 (54%)</td>
<td>8 (47%)</td>
<td>0.78</td>
</tr>
<tr>
<td>mild polyposis</td>
<td>37 (63%)</td>
<td>12 (71%)</td>
<td>0.77</td>
</tr>
<tr>
<td>ASA triad</td>
<td>5 (9%)</td>
<td>3 (18%)</td>
<td>0.37</td>
</tr>
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<td>smoking</td>
<td>4 (7%)</td>
<td>3 (18%)</td>
<td>0.18</td>
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</tbody>
</table>

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<tr>
<th>endoscopy</th>
<th>responders n=64</th>
<th>non-responders n=12</th>
<th>p-value Fischer exact test</th>
</tr>
</thead>
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<tr>
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<td>2 (17%)</td>
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<td>asthma</td>
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<td>6 (50%)</td>
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<tr>
<td>mild polyposis</td>
<td>39 (61%)</td>
<td>10 (83%)</td>
<td>0.19</td>
</tr>
<tr>
<td>ASA triad</td>
<td>5 (8%)</td>
<td>3 (25%)</td>
<td>0.11</td>
</tr>
<tr>
<td>smoking</td>
<td>4 (6%)</td>
<td>3 (25%)</td>
<td>0.07</td>
</tr>
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</table>

Side effects
No serious adverse events were observed. Three complaints possibly related to long-term low-dose antibiotics were reported. One patient treated with the macrolide azithromycin mentioned mild muscle-aches during the prolonged course, without a reason to end the
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administration. In the 5 patients with long-term low-dose clarithromycin of the macrolide group, there were 2 patients complaining of mild, reversible skin rash. In all 3 events there was no reason to end the course. No adverse events were reported in the trimethoprim-sulfamethoxazole group.

DISCUSSION

In the majority of patients suffering from recalcitrant CRS, no underlying etiology is found. Suspects under attention are: superantigens, fungal infections, inflammation of the underlying bone, biofilm, and intracellular presence of bacteria in the epithelial cells of the middle meatus mucosa. Long-term low-dose antibiotics are believed to be useful in the treatment of recalcitrant CRS, not only in the battle against microorganisms, but also because of the pretended immunomodulatory qualities. The mechanism behind this is not well understood, but probably involves down-regulation of the local host immune response as well as a downgrading of the virulence of the colonizing bacteria. However, there is lack of evidence in terms of placebo-controlled, double-blind, randomized trials.

The antibiotics evaluated in this present study, trimethoprim-sulfamethoxazole and macrolides, have more or less the same antibiotic spectrum. This includes the coverage of the sinonasal colonizer Staphylococcus aureus, but Pseudomonas aeruginosa for example is not covered. Although trimethoprim-sulfamethoxazole is prescribed long-term low-dose in diseases such as Wegener’s disease or granulomatous disease, urinary and respiratory tract infections and for prophylaxis and treatment of Pneumocystis carinii infection, we did not find any data in literature on the prolonged usage in patients with recalcitrant CRS.

In the scarce amount of literature on long-term low-dose antibiotic treatment in patients with recalcitrant CRS, most data report on macrolides. Clinical studies support the view that macrolides are likely to be beneficial in most patients who have CRS. Besides their ability to accumulate in inflammatory cells at concentrations up to several 100-folds higher than concentrations in extracellular fluids, macrolides are known to increase mucociliary transport, reduce goblet cell secretion, accelerate apoptosis of neutrophils, reduce expression of cell surface adhesion molecules, alter structure and function of biofilm, and macrolides have shown to decrease levels of IL-5, IL-6, IL-8, GM-CSF, TGF-β, and TNF-α. There is also evidence in vitro showing that macrolides reduce the virulence and tissue damage caused by chronic bacterial colonization without necessarily eradicating the bacteria.

In this presented group of patients, we found that 1) patients responded well to the long-term low-dose antibiotic treatment; 2) response decreased slightly over time after cessation of the antibiotic treatment, but results were still satisfactory at the end of the 5 months follow-up; 3) there was no difference between the two evaluated antibiotic families. A substantial reduction in sinonasal symptoms of 78%, and an improvement of mucosal conditions of 84% was found. More detailed statistical analysis comparing both antibiotics families, demonstrated no significant differences between them. It is therefore not possible, based on these data, to elect one antibiotic over the other. In the performed subgroup
analysis we evaluated allergy, asthma, mild nasal polyposis, ASA triad and smoking. Although no statistical significant differences were found, it is remarkable to find a higher percentage of allergies in the responding group. Perhaps this could be a pointer to the immunomodulatory effects of the antibiotics. Another observation was the higher incidence of smoking in the non-responders group. This puts the importance of encouragement of smoking again into the spotlight.

Multiple comments can be made on this study. We performed a retrospective evaluation with many shortcomings and pitfalls coming along with it. Before we discuss some of them, we stress the recalcitrant nature of CRS in this studied population, for which all conventional treatment options have proven to be insufficient. Patients suffering from this recalcitrant disease are hard to motivate to participate in a placebo-controlled trial, because they do not want to risk the chance on placebo. For that reason we felt it was useful to do this retrospective analyses were all patients that received antibiotics could be evaluated. However, the absence of a control-group in this evaluation inhibits the development of strong conclusions. What would be the result of placebo compared with trimethoprim-sulfamethoxazole and macrolides? In the first performed, 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. In the second performed RCT on the efficacy of an equal dose azithromycin in patients with recalcitrant CRS, no significant difference between azithromycin and placebo was found either (see chapter 3, part 2). However, contrary to both placebo-controlled studies, the present study and the non-placebo-controlled study from Ragab, demonstrate a significant positive effect on some patients. In the placebo-controlled studies both the treatment and the placebo did not have a significant effect on the symptomatology nor the endoscopic results. Especially in our own study, that we know was performed in a group of patients partly overlapping with the presented population of this study, this difference was very clear: very little effect of macrolide in the placebo-controlled study and a significant effect of the macrolide in the non-placebo controlled trial. We hypothesize that the selection of patients that are willing to participate in a randomized placebo controlled trial differs substantially from the population we treat in daily clinical practice. This is a phenomenon that has been discussed in recent years especially in trials dealing with serious chronic disease. In an attempt to create a homogeneous population, researchers tend to use strict inclusion criteria. This may lead to a selection bias of the enrolled patients, who may substantially differ from the population encountered in clinical practice.

Another comment on this study could be the appropriate dosage of the antibiotics. Some clinicians start a prolonged treatment with the standard dose for treating acute infections and after 2 weeks lower the dose to half. This was done for trimethoprim-sulfamethoxazole and clarithromycin. Azithromycin has a longer half-life time, which justifies a dosage once weekly. Before starting a long-term low-dose antibiotic treatment, the patient has to be informed that it takes 4 to 8 weeks for the treatment to have an effect, and that a proper evaluation cannot be performed until the treatment period has covered 10 to 12 weeks. It is suggested that if the treatment is successful it should be prolonged for several months. We normally start with an arbitrary period of at least 3 months.
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The follow-up of around 5 months could be another point of criticism. The reader should keep in mind that recalcitrant CRS in this group of patients is hard to combat and most patients continuously demand new steps in treatment process. On the other hand, patients who did well on the prolonged medical therapy were sent back to their secondary care centres.

Patients were seen by a team of rhinologists at the outpatient clinic. Although they work closely together, follow protocols and frequently discuss individual patients, there is always the risk of inter-observer bias. While collecting the data for this retrospective evaluation, patient records were studied at least by two of the authors. Different opinions were thoroughly discussed and in doubt the most negative opinion (e.g. between moderate and good response) prevailed.

In the debate on prolonged administration of antibiotics, the development of resistant bacteria is a returning item. To date an all-including conclusion cannot be made, but it is suggested that the risk of selecting resistant bacteria is low.\textsuperscript{19} In this present investigation we did not evaluate bacterial culture results consistently and we consequently cannot present data on resistance development in this whole group. In the recently accepted RCT that we have discussed above, we did not find a relevant increase of resistance in the cultured bacteria.

Although long-term low-dose antibiotic treatment seems to be a promising option, as we observe in a selection of patient at the outpatient clinic, it is too early to formulate firm conclusions. An important target for this future work could be the identification of the group of responders or poor prognostic factors in CRS patients. Suzuki et al. reported on elevated IgE levels and substantial eosinophilia in smear, tissue or blood as being poor prognostic factors.\textsuperscript{61} In some studies, the presence of nasal polyps also has been reported as being unfavourable for the efficacy of long-term low-dose antibiotic treatment.\textsuperscript{19} Further identification of subgroups is necessary. In our opinion long-term low-dose treatment could be a promising alternative treatment option in the battle against recalcitrant CRS in a selected group of patients. Especially when the patient is not motivated for additional surgery or significant co-morbidity increases the operation risks. It can also help patients who suffer from CRS complaints during a particular season of the year, and create optimal conditions for paranasal recovery in the postoperative period. However it is still difficult to tell which patient would benefit from this treatment and more research in this field is urgently required.

Acknowledgments

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LONG-TERM LOW-DOSE ANTIBIOTICS IN RECALCITRANT CHRONIC RHINOSINUSITIS

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