Recalcitrant chronic rhinosinusitis. Difficulties in diagnosis and treatment
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Nebulized bacitracin/colimycin: a treatment option in recalcitrant chronic rhinosinusitis with Staphylococcus aureus? A double-blind, randomized, placebo-controlled, cross-over pilot study

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ABSTRACT

Introduction
Despite optimal medical therapy and endoscopic sinus surgery there still remains a group of unfortunate patients suffering from exacerbations of recalcitrant chronic sinusitis. We have performed 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.

Patients and Methods
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.

Results
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.

Conclusion and discussion
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.
INTRODUCTION

Chronic Rhino Sinusitis (CRS) is a common chronic condition with an estimated prevalence between 5-15% of the population in Europe and the United States.\(^1,2\) Contrary to its high prevalence and substantial costs for society, many uncertainties exist around the pathogenesis of CRS. Biofilm is suggested to be an etiological factor of CRS in addition to anatomical, immunological, viral and bacterial causes, and has been reviewed recently.\(^3\) Biofilms are structured communities of adherent micro-organisms encased in an Extracellular Polymetric Substance (EPS). They continually present antigen, resulting in chronic inflammation. Characteristics of biofilm, resemble important features of the clinical course of recalcitrant CRS. Analogous to its predominance in nasal CRS cultures, Staphylococcus aureus (S. aureus) has been linked to biofilm.\(^4,5\) Patients described in this study suffer from recalcitrant CRS with persistent nasal colonization of S. aureus.

The medical treatment regime for CRS consists of a combination of nasal saline irrigations, decongestants, nasal and systemic steroids, and courses of antibiotics. Patients with CRS resistant to this medical regime are treated with Endoscopic Sinus Surgery (ESS). Despite the success rate for a primary ESS procedure of around 80%,\(^6,7\) and other ongoing advances like new generations of antibiotics, there are still unfortunate patients with recalcitrant CRS. Even repeat ESS in combination with maximal medical treatment does not reduce symptoms. Radical surgery has been suggested as a last refuge for these cases.\(^8,9\) In general practice, prolonged antibiotics are frequently prescribed in an attempt to control recalcitrant CRS.\(^10\) Although widely accepted, this strategy is empirical and based in part upon culture reports available in current literature. Disadvantages of prolonged antibiotic administration include allergic reactions, gastrointestinal and hepatic disturbances, nephrotoxicity, photosensitivity, infection of the infusion site, embolism, ototoxicity, and resistance of the pathogenic micro-organisms. Topical application of antibiotics directly to the target site has been suggested to prevent these adverse effects of prolonged systemic administration and avoid frequent blood tests. In patients with polyposis, topical administration of nasal steroids has been well accepted for years as a treatment modality.

It is interesting that so few studies have been conducted to explore the therapeutic option of topical nasal antimicrobials in the treatment of recalcitrant CRS. In 1999, Leonard et al. reported good reduction of symptoms with little bacterial resistance when using ceftazidime added to saline irrigation in post surgical CRS patients.\(^11\) In a prospective study, Kamiyoe et al. reported on 28 patients treated with fosfomycin nebulization 3 times a week for a period of 4 weeks. Improvement in terms of objective symptoms and endoscopic findings was rated as at least fair in about 60% of patients, except for the amount of secretion. Postnasal drip improved in 88% of the patients.\(^12\) Vaughan et al. evaluated the effect of nebulization of several antimicrobials over a period of 3 months in 42 patients with CRS. They reported significant improvements for posterior nasal discharge, facial pain and emotional consequences. There was also an increase of the “disease-free interval period”.\(^13\) In a retrospective evaluation, Scheinberg et al. reported on the effect of nebulized antibiotics for the treatment of acute exacerbations of CRS in 41 patients. Eighty-three per cent of the patients improved on nasal obstruction, facial pain, rhinorrhea and malaise after administration of nebulized antibiotics. The researchers concluded that nebulized antibiotics should be considered for all patients with CRS who have undergone...
ESS and who have failed to respond to oral antibiotics or who do not tolerate them.\(^{14}\) Recently, Antunes et al. reported on the dose-dependent effects of topical tobramycin in an animal model of Pseudomonas aeruginosa sinustis. They noted that as opposed to normal saline irrigations, topical tobramycin led to a significant improvement in the degree of infection in this animal model.\(^{15}\)

Other studies, most placebo controlled, report less favourable data. In a randomized double-blind, placebo-controlled trial analyzing 50 patients with CRS, Sykes et al. evaluated the efficacy of nasal sprays with combinations of dexamethasone-tramazoline-neomycin, dexamethasone-tramazoline, or matched placebo. No significant difference in response between the active preparations with or without antibiotic was found after 2 weeks of treatment.\(^{16}\) Kobayashi and Baba used an ultrasound-type inhaler and studied therapy with aminoglycoside, fosfomycin, and cefmenoxime 3 times per week. Their findings suggested that in patients without previous sinus surgery, the main effect of the nebulized medications was in the nose, with only an indirect effect on the maxillary sinuses: no experimental evidence was found of antibiotic penetration into the maxillary sinus.\(^{17}\) In a randomized, double-blind trial Desrosier et al. reported that both tobramycin-saline solution and aerosolized saline solution led to equal improvements in quality of life (QoL), symptomatology, and endoscopic aspects of the nasal mucosa. The addition of tobramycin appears of minimal benefit.\(^{18}\)

Despite these reports, the body of evidence is too small and too diverse to draw definitive conclusions about the effectiveness of nebulizing antibiotics in treating recalcitrant CRS. Motivated by the intention to find alternative treatment options for patients with CRS not responding to conventional treatment modalities, we performed this pilot study. We investigated the efficacy of nebulized bacitracin/colimycin in combination with 2 weeks of oral levofloxacin, in a group of CRS patients for whom there are currently no other medical or surgical therapeutic alternatives. Our main aim was to determine whether topical nebulized antibiotic therapy in combination with oral antibiotics, improves CRS symptoms and prevents relapse of disease better than saline-based placebo.

**PATIENTS AND METHODS**

**Patients**

This study was initiated in 2004 at the Erasmus Medical Centre Rotterdam and was completed in 2007 at the Academic Medical Centre (AMC) Amsterdam (the Netherlands). The local ethics committee's of these tertiary referral centres, approved the study. Informed consent was obtained from all subjects. Patients of at least 18 years of age were eligible for the trial when they met the aspects of the clinical diagnosis of recalcitrant CRS, combined with nasal colonization with S. aureus. Recalcitrant CRS was defined as inflammation of the nose and paranasal sinuses characterized by 2 or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) in combination with facial pain/pressure and/or reduction or loss of smell for more than 12 weeks. These symptoms should be confirmed with nasal endoscopy and CT scan evaluation.\(^{19}\) Patients included in this evaluation all underwent several technically successful ESS procedures in combination with optimal medical therapy. Despite adequate communication between the sinuses and nasal cavity observed
during endoscopy, patients continued to suffer from recurrent exacerbations of CRS, not responding to further medical therapy. We defined these patients therapy resistant when symptomatology and a positive nasal culture for S. aureus returned, despite 2 previous attempts to treat the disease with appropriate antibiotics (at least 2 weeks) and nasal saline irrigation. Other eligibility criteria included an adequate command of the Dutch language and sufficient contraceptive precautions when childbearing potential. Exclusion criteria were: extensive obstructive nasal polyposis, known immune suppression or deficiency, sinonasal neoplasm, severe anatomical defects of the nose or paranasal sinuses, other underlying diseases like cystic fibrosis, congenital mucociliary problems, and vasculitic or granulomatous disorders.

Study
This pilot study was designed as a randomized, placebo-controlled, double-blind, cross-over study to evaluate the additional effect of bacitracin/colimycin nebulization with the RhinoFlow. Bacitracin is an inhibitor of the cell wall synthesis, and has in vitro activity against even methicillin resistant S. aureus. It was also shown to be active in suppressing S. aureus nasal carriage. The applied dose bacitracin/colimycin (830/640 μg/ml) 8 ml twice daily is significant higher than the Minimal Inhibitory Concentration (MIC) range for most predominant species of S. aureus described in literature. A saline-based solution containing no active components served as placebo and was identical in appearance to the verum medication. Combined with the nasal irrigation for 8 weeks, both arms started with levofloxacin 500 mg twice daily for 2 weeks. Levofloxacin is effective against a number of gram-positive and gram-negative bacteria, and is prescribed empirically for a wide range of infections (e.g. upper airway infections, pneumonia, and urinary tract infection). The administration of levofloxacin was used to treat the acute CRS exacerbation and reduce the S. aureus load.

After 8 weeks of nebulization, a wash out period of at least 4 weeks was initialized before the study could continue conform to other reports. The washout period included a period of a minimum of 2 weeks in which patients were instructed to evaluate CRS symptoms. After these 2 weeks, patients contacted the investigating doctor, when evident symptomatology reappeared. Evaluation by the investigating otorhinolaryngologist including a nasal culture was performed within another 2 weeks. The second phase could only start when nasal S. aureus colonization was confirmed. Patients who did not experience relapse of CRS did not enter the second phase of the trial. During the second treatment phase of 8 weeks, both arms again started nebulizing with the provided study medication, combined with levofloxacin for 2 weeks. Patients, who used bacitracin/colimycin in the first half of the study, were given placebo in the second phase and vice versa. The study design flow chart is shown in Figure 1.
**Figure 1. Design and Patient Flow (Cross-Over Study).**

**Nebulizer**
RhinoFlow (Respironics, Inc., Cedar Grove, NJ, USA), a system available commercially for generating nebulized aerosol to irrigate the nasal cavity and sinuses, was used to apply the study medication. The RhinoFlow Nasal Wash and Sinus System consists of a portable, sealed, electric, lubricant-free, piston compressor and a micronizer chamber. It generates particles between 20 and 30 μm, which is in the range where distribution into the sinuses is best achieved. The nebulized study medication was stored in the refrigerator and self-administered at home.
Outcome measures
Severity of disease was measured using VAS scores, a Disease-Specific Symptom Score and the SF-36 questionnaire. The VAS score grades symptoms on a 0-10 cm line. Zero (at the left of the line) represents no complaints and 10 (at the right of the line) the worst possible symptoms. The following symptoms were assessed: nasal obstruction, rhinorrhea, postnasal drip, crusts, headache, facial pain, smell disturbance, nasal pain, nosebleeds, fever, malaise, fatigue. The Disease-Specific Symptom Score evaluates the following fourteen items by grading them from 0 to 10: nasal obstruction, rhinorrhea, postnasal drip, crusts, headache, facial pain, feeling of fullness, smell disturbance, nose bleeds, tears, tooth pain, vision disturbance, coughing, and asthma. SF-36 is a widely used, reproducible, and valid generic quality of life measure, which evaluates general health status by grouping 36 item responses into 8 health domains: Physical Function (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH). Endoscopic findings were also evaluated.

Statistical analysis
To investigate the comparative efficacy of bacitracin/colimycin and placebo, we plotted the change in outcome (end of treatment minus pre-treatment measurement) for both these arms in one graph. Because of the cross-over design, each patient was depicted twice (once in the placebo, and once in the active group) unless they did not participate in the second part. The mean change was compared using both a paired t-test (only measurements of patients that did cross-over) and an unpaired t-test (analysis of all available measurements). Statistical analysis of the data was performed with the software SPSS, version 12.1, and GraphPad Prism, version 4.

RESULTS
Patients
Fourteen patients (6 male, 8 female) were enrolled in this study. The mean age was 52 years (range, 33-87 years). The trial population underwent a median of 4 sinonasal operations (range, 2 to 9 procedures) before the start of this study. Two patients were smokers. Three of them only completed the first half of the study (i.e. the first 8 weeks). One patient from the bacitracin/colimycin group did not notice an aggravation of symptoms during the wash-out period and therefore did not participate in the second phase of the trial. One patient from the placebo arm underwent symptom reduction after the first treatment period, but did not want to continue the study without medical reason. Another placebo-group patient reported no noticeable symptom reduction and decided to end participation after the first 8 weeks. The nebulized study medication was well tolerated and no side effects were reported during the complete course of the trial in any of the patients. Patient compliance and medication storage was checked during every visit and appeared optimal.

Visual analogue scale
Compared to the pre-treatment scores, nasal crusts (p=0.04) and facial pain (p=0.03) were significantly reduced when treated 8 weeks with bacitracin/colimycin. A comparable reduction was found in the saline-based placebo arm (p=0.03 and p=0.02, respectively).
Because of the small sample size and the limited power of formal statistical tests, the change in scores between post- and pre-treatment (delta) for both the bacitracin/colimycin (B) and placebo (P) group was visualized in scatter plots to detect any potential pattern in scores. Every dot represents a patient. Figure 2 shows the results per symptom. For most items, a reduction in symptom severity was noted in both the bacitracin/colimycin and the placebo group. However, no significant difference was found between the two arms (bacitracin/colimycin (B) vs. placebo (P)). The associated t-test results are summarized in Table 1. Analysis of added complementary symptom scores like crusts, postnasal drip and rhinorrhea in different combinations did not gain any additional insights.

**Table 1. VAS score (p-values).**

<table>
<thead>
<tr>
<th></th>
<th>t-test</th>
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<tbody>
<tr>
<td>nasal obstruction</td>
<td>0.38</td>
</tr>
<tr>
<td>rhinorrhea</td>
<td>0.84</td>
</tr>
<tr>
<td>postnasal drip</td>
<td>0.22</td>
</tr>
<tr>
<td>crusts</td>
<td>0.64</td>
</tr>
<tr>
<td>headache</td>
<td>0.90</td>
</tr>
<tr>
<td>facial pain</td>
<td>0.53</td>
</tr>
<tr>
<td>smell disturbance</td>
<td>0.72</td>
</tr>
<tr>
<td>nasal pain</td>
<td>0.50</td>
</tr>
<tr>
<td>nose bleeds</td>
<td>0.36</td>
</tr>
<tr>
<td>fever</td>
<td>0.25</td>
</tr>
<tr>
<td>malaise</td>
<td>0.07</td>
</tr>
<tr>
<td>tiredness</td>
<td>0.42</td>
</tr>
</tbody>
</table>
**Figure 2.** Overview of changes in VAS scores for different symptoms (end-treatment-score minus pre-treatment score). B = bacitracin/colimycin (left); P = placebo (right)

- **VAS nasal obstruction**
- **VAS rhinorrea**
- **VAS postnasal drip**
- **VAS crusts**
- **VAS headache**
- **VAS facial pain**
- **VAS smell disturbance**
- **VAS nasal pain**
- **VAS nose bleeds**

**Disease-Specific Symptom Score**

Most symptoms improved over time. Nasal crusts were significantly reduced compared to the pre-treatment score in both the bacitracin/colimycin arm and the placebo arm (B: \( p=0.002; \) P: \( p=0.002 \)). Feeling of fullness (\( p=0.009 \)) and nosebleeds (\( p=0.04 \)) were reduced in the verum-arm. To compare the two study arms, delta scores were again calculated, and visualized in scatter plots. There was no significant difference between the bacitracin/colimycin and placebo group. Table 2 shows the p-values. Once again, analysis...
of summarization of complementary symptoms scores like crusts, postnasal drip, and rhinorrhea in different combinations failed to generate additional information.

Table 2. Disease-Specific Symptom Score (p-values)
bacitracin/colimycin vs. placebo

<table>
<thead>
<tr>
<th>Symptom</th>
<th>p-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>nasal obstruction</td>
<td>0.85</td>
<td>ns</td>
</tr>
<tr>
<td>rhinorrhea</td>
<td>0.29</td>
<td>ns</td>
</tr>
<tr>
<td>postnasal drip</td>
<td>0.26</td>
<td>ns</td>
</tr>
<tr>
<td>crusts</td>
<td>0.30</td>
<td>ns</td>
</tr>
<tr>
<td>headache</td>
<td>0.45</td>
<td>ns</td>
</tr>
<tr>
<td>facial pain</td>
<td>0.45</td>
<td>ns</td>
</tr>
<tr>
<td>feeling of fullness</td>
<td>0.45</td>
<td>ns</td>
</tr>
<tr>
<td>smell reduction</td>
<td>0.75</td>
<td>ns</td>
</tr>
<tr>
<td>nose bleed</td>
<td>0.92</td>
<td>ns</td>
</tr>
<tr>
<td>tears</td>
<td>1.00</td>
<td>ns</td>
</tr>
<tr>
<td>tooth pain</td>
<td>0.65</td>
<td>ns</td>
</tr>
<tr>
<td>vision disturbance</td>
<td>0.92</td>
<td>ns</td>
</tr>
<tr>
<td>coughing</td>
<td>0.62</td>
<td>ns</td>
</tr>
<tr>
<td>asthma</td>
<td>0.44</td>
<td>ns</td>
</tr>
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Quality of life results
Before treatment, the subjects with CRS had significantly poorer QoL scores in all SF-36 domains compared to the general Dutch population. The lowest score was for Role Physical. General Health, Vitality, and Social Functioning, also scored below 50. Figure 3 shows the SF-36 scores for the bacitracin/colimycin group compared with the placebo group. Most items improved compared with the situation before treatment in both the treatment and placebo group. None of the improvements were significant compared with baseline. Role Physical and Vitality showed a tendency towards significance. Compared with the scores for the general Dutch population, the scores for most subdomains remained lower in both groups after completion of treatment. Additional analysis to investigate significant difference between the bacitracin/colimycin group and placebo did not reveal any significant results.
Endoscopic findings
Nasal endoscopy was performed during the outpatient clinic visits. The findings were subdivided in different categories: nasal obstruction, rhinorrhea, crusts, polyps, color of mucosa, and postnasal drip. Items were scored on a 3-point scale (absent, mild and severe). Mucosa color improved significantly in the bacitracin/colimycin group (p=0.0001). No significant differences were found between the 2 treatment modalities.

DISCUSSION
The complete pathophysiology of refractory CRS has not been unravelled, but seems to be complex, multifactorial, and continues to be debated in literature. In addition to host characteristics, including anatomical variations, allergy, ciliary dysfunction, and IgG subclass deficiencies, external factors like pollution, fungi, viruses, and bacteria all seem to play a role. In many bacteriological culture studies, S. aureus has been found to be a predominant species. Despite the consistency of culture results positive for S. aureus, there is no consensus about whether its presence is of pathogenic importance. Recently some studies have reported on the intracellular presence of S. aureus in the epithelial cells of the middle meatus mucosa. These intracellular colonies may represent a reservoir for recurrent episodes of CRS that are protected from host defense mechanisms and antibiotic treatment. The secretion of various enzymes and toxins feeds the inflammatory reaction and preserves the recalcitrance of the disease. Moreover S. aureus has been discussed in literature because of its superantigen potentials and their apparent link to biofilm. Patients in this recent study were selected for the presence of S. aureus in the middle meatus culture, performed during nasal endoscopy. Its presence was not an outcome measure in this investigation, but served as an indicator of relapse of disease.
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Therapy in patients suffering from recalcitrant CRS consists of repetitive ESS procedures combined with maximal medical treatment. Despite this treatment strategy, some unfortunate patients continue to endure invalidating sinonasal complaints. Ostia of the sinuses play a pivotal role in the disease. The goals of surgery in the recalcitrant cases are not necessarily curative. The intention is rather to reduce the severity of symptoms by improving the ostia-opening and removing diseased mucosa. Nasal endoscopy in our subjects revealed open neo-ostia, providing a sufficient way for drainage and aeration. Despite this freely communicating sinonasal complex, inflammation with mucosal oedema, nasal secretion and crusts stubbornly persists.

As mentioned in the introduction, it is interesting that so few studies have been conducted to explore the therapeutic role of topical nasal antimicrobials. Several studies indicate that the local application of antibiotics has a beneficial effect.11-15 Others have found that nasal irrigation is useful, but addition of antibiotics represents no supplementary advantage.16-18 Goh and Goode, and Elliott et al. have reviewed the limited data; their overall conclusion was that the role of nasal antimicrobial therapy, although promising, was not established.39,40

Our pilot study revealed that patients with therapy resistant CRS, many symptoms have a tendency to decrease compared with the pre-treatment period after using the nebulizer in combination with levofloxacin. None of the analyses comparing the bacitracin/colimycin group with placebo however identified significant differences. Therefore this study has not confirmed any additional effect of the locally administered antibiotics. A post-hoc sample-size calculation was conducted to estimate the minimum size of groups needed to detect a statistical difference (two-tailed, $\alpha = 0.05$) and a power of 0.80. To detect differences in the CRS important symptoms, each group would have to include at least a minimum of 126 patients.

The reason to evaluate bacitracin/colimycin nebulized with the RhinoFlow was the observation of favourable results in a group of CRS patients treated in this manner. The primary goal of antimicrobial therapy is to provide an adequate concentration of a drug at the site of infection to eradicate bacteria and produce a clinical cure. However, the targeted pathogen must be sensitive to the chosen medication. A suboptimal dose could make it more likely that bacteria will survive and adapt through acquisition of drug resistance.40 Factors like optimal dose, absorption rate into sinus mucosa, and dosing regimen have not yet been established for nebulized bacitracin/colimycin. Our dosage was well above the target MIC levels described in literature. We did not try to increase the dose or frequency of administration. The results of this study suggest that the current concentration or administration frequency may be too low to be effective against S. aureus. We did not conduct any closer investigation on the sensitivity of the S. aureus.

One might wonder why saline solution itself is as effective as the antibiotic treatment. The mechanically cleansing of the sinus surface by the nebulized solution appears to be relevant. Saline irrigation has been shown previously to be effective in improving sinonasal disease, both subjectively and objectively.41,42 The regular irrigation reduces the viscosity of the secretion and improves the mucocilliary transport. The additional reduction of mucosal oedema, microbes, toxins and inflammatory substances could also be beneficial. It is opted that irrigation may have a role in the mechanical removal of biofilm.16,41
Could the course of levofloxacin confound the outcome of the nebulized medication? As discussed in the definition, the patients proved to be therapy resistant after at least 2 courses of antibiotics combined with nebulized saline. Levofloxacin has an estimated half-life of 6-8 hours and was used in both arms. In our opinion the beneficial effect of levofloxacin was unlikely to camouflage the true effect of the nebulized medication over the period of 8 weeks. However we cannot prove this with the present data.

Is the nebulizer an adequate mode of administration? Efficacy reports in literature about this local distribution method are contradictory. Negley et al. demonstrated direct delivery of medication to the sinus using the Rhinoflow. Wormald et al. demonstrated that the nebulizer is adequate in terms of delivery. Olsen et al. reported that the nebulizer was less effective than positive- and negative-pressure irrigation of the nose. Miller et al. showed that bulb syringe irrigation of the nose was statistically superior to the nebulizer. Future research should also keep other ways of topical administration in mind.

A variety of further comments must be made about the study structure before arriving at more definite conclusions. An obvious shortcoming is the low number of included patients. A major reason for this limited group size is the low prevalence and the severity of disease in this studied population. We describe a group of “nasal cripples”, patients who were unsuccessfully treated with repeated ESS in combination with maximal medical therapy. We compared the quality of life scores of this studied population with the therapy resistant cases of the population treated with Denker’s procedure (see chapter 4), recently published by our group. The scores were remarkably similar and significantly worse than the scores of the general population (Figure 3). Turning to the study structure, it should be pointed out that, in cross-over setting, effect of one treatment may “carry over” and alter the response to subsequent treatments. The usual approach to prevent this is to introduce a washout period (no treatment) between consecutive treatments, which is long enough to allow the effect of the treatment to wear off. This was done in this study. An additional drawback of the cross-over setting is the selective lost to follow-up. Patients who feel better may decide to end participation, as may the patients who fail. The short duration of the follow-up also merits mention.

In conclusion, we found that nebulizing the nose and paranasal sinuses had a beneficial effect, on several CRS symptoms. Our results did not find any additional effect when bacitracin/colimycin was added to the nebulized solution. Definite recommendations cannot be made on the basis of this pilot study. Future research should join forces and randomized, multicentre studies are needed to explore this field of treating recalcitrant CRS and providing longer disease-free intervals for this group of patients.
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REFERENCE LIST