

# Topical antifungal treatment of chronic rhinosinusitis with nasal polyps: A randomized, double-blind clinical trial

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**Background:** Recently, fungal elements were suspected to be the causative agent of chronic rhinosinusitis, and benefits of topical amphotericin B therapy have been reported.

**Objective:** The effects of amphotericin B versus control nasal spray on chronic rhinosinusitis were compared in a double-blind, randomized clinical trial.

**Methods:** Patients with chronic rhinosinusitis were administered 200  $\mu$ L per nostril amphotericin B (3 mg/mL) or saline nasal spray 4 times daily over a period of 8 weeks. The response rate, defined as a 50% reduction of pretreatment computed tomography score, was the primary outcome variable. Additional outcome variables included a symptom score, a quality of life score, and an endoscopy score. Before and after treatment, nasal lavages were pretreated with dithiothreitol and examined for fungal elements by PCR and standard culture techniques.

**Results:** Seventy-eight patients were included, and 60 patients finished the study per protocol. In the control group, no positive response (0 of 32) was observed, and 2 of 28 patients responded in the amphotericin B group ( $P > .2$ ). The symptom scores were distinctly worse after amphotericin B therapy ( $P < .005$ ). The other parameters investigated did not differ remarkably between the treatment groups.

**Conclusion:** Nasal amphotericin B spray in the described dosing and time schedule is ineffective and deteriorates patient symptoms. (J Allergy Clin Immunol 2004;113:1122-8.)

**Key words:** Nasal polyps, amphotericin B, antifungal agents, sinusitis, fungi

The etiology of chronic rhinosinusitis (CRS) is unclear. Recently it has been suggested that a fungus-mediated process is the primary cause of CRS with and without polyps.<sup>1</sup> In brief, the authors stated that inhaled fungal elements become entrapped in the sinunasal mucus, causing eosinophils to shift from respiratory mucosa into the lumen by a yet unknown mechanism. Eosinophils then cluster around and attack the fungal elements. During this

## Abbreviations used

AFRS: Allergic fungal rhinosinusitis

AMB: Amphotericin B

CRS: Chronic rhinosinusitis

RQL: Rhinosinusitis quality of life score

process, they release toxic mediators resulting in secondary mucosal inflammation.

Consequently, elimination of the supposed causative agent should improve the course of disease. Two studies on nasal antifungal treatment of CRS in immunocompetent hosts have been published. In 1 unblinded and uncontrolled study, 74 patients with nasal polyps resistant to standard treatment including nasal steroids and nasal lavages were recruited. During the 4-week study period, the patients performed nasal washing with 20 mL distilled water containing amphotericin B (AMB) twice daily in addition to the prestudy treatment. Using an endoscopic staging system, an overall cure rate of 39 percent was recorded, favoring patients with less severe disease.<sup>2</sup>

In a recently published observational study, 51 patients with different forms of CRS, including allergic fungal rhinosinusitis (AFRS), were treated with 20-mL nasal lavages containing AMB (0.1 mg/mL) twice daily for at least 3 months. Concomitant nasal or systemic corticosteroid therapy was continued in the same dosage as before study entry. After treatment, nasal polyps had endoscopically disappeared in 35% of patients, and 49% reported complete relief of symptoms.<sup>3</sup>

Both observational studies were unblinded and uncontrolled and thus susceptible to observer bias.<sup>4</sup> Moreover, in both studies, patients obtained their antifungal treatment on the basis of therapeutic nasal lavages, an active treatment for CRS.<sup>5</sup> Because both studies lacked a control group, possible effects of the antifungal treatment could not be differentiated from the effects of the nasal lavages.<sup>6</sup>

In this study, the effects of locally administered AMB on CRS severity were assessed in a prospective, double-blind, randomized, placebo-controlled pretest-posttest design. AMB was administered as a nasal spray to avoid interference with possible effects of nasal lavages. The response rate, defined as a 50% reduction of pretreatment computed tomography score, was the primary outcome variable. Secondary outcome variables included a

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**TABLE I.** Inclusion and exclusion criteria for study recruitment

|                                                         |
|---------------------------------------------------------|
| Inclusion criteria                                      |
| • Age >18 y                                             |
| • Recent CT scan of paranasal sinuses                   |
| • Symptom score >14*                                    |
| • Endoscopy score >2 <sup>†</sup>                       |
| • CT score >19 <sup>‡</sup>                             |
| Exclusion criteria                                      |
| • Current participation in other clinical study         |
| • Pregnancy or breast-feeding                           |
| • Mental impairment or severe illnesses                 |
| • Hypersensitivity to study medication                  |
| • History of immotile cilia syndrome or cystic fibrosis |
| • Urgent need for or recent paranasal surgery           |
| • Recent start on                                       |
| Specific antiallergic immunotherapy                     |
| Corticosteroid therapy, antihistamines                  |
| Acetylsalicylic acid desensitization                    |
| • Discontinuous study medication intake                 |
| • Antimycotic or immunosuppressive therapy              |
| • Clinical suspicion of AFRS                            |

\*Sum of values for nasal blockage, facial pain, and smell disturbance, maximum = 30.

<sup>†</sup>Maximum = 6.

<sup>‡</sup>Maximum = 40.

symptom score, a rhinosinusitis quality of life score (RQL), and an endoscopy score. To assess fungal involvement, the detection rate of fungal elements in diagnostic lavages was determined before and after treatment. Moreover, it was assessed whether successful fungus eradication had a beneficial effect.

## METHODS

### Patients

Between April 2001 and April 2003, patients with nasal polyps referred for paranasal sinus surgery were screened. To achieve a homogenous study group, only patients exceeding a minimum symptom score, endoscopy score, and CT score were included. Patients with impaired host defense or those clinically suspicious for AFRS as defined by Bent and Kuhn<sup>7</sup> were excluded. Further inclusion and exclusion criteria are detailed in Table I. The study was approved by the ethics committee of the University of Ulm (Nr.82/2001). All patient-related study data were recorded in case report forms and internally monitored for accuracy, completeness, and legibility at regular intervals.

### Study medication

Active drug and control sprays were manufactured by the pharmacy of the University Hospital of Ulm. They were indistinguishable in color, taste, smell, and nasal sensations during application. The active drug contained AMB 3 mg/mL and sodium deoxycholate 2.46 mg/mL (Bristol-Myers Squibb, München, Germany) in sodium phosphate buffered 5% glucose solution (DeltaSelect GmbH, Pfullingen, Germany) at pH 7.5. Control spray contained tartrazine 0.02% (wt/vol; Synopharm GmbH, Barsbüttel, Germany), chinin sulfate 0.015% (wt/vol; Caesar & Loretz GmbH, Hilden, Germany), 1-(4-sulfo-1-phenylazo)-2-naphthol-6-sulfo acid 0.02% (wt/vol; Synopharm GmbH), and (3-sn phosphatidyl) choline 1.0% (vol/vol; (Lipostabil N; Nattermann & Cie, Köln, Germany) in

glucose solution 5% (DeltaSelect GmbH) at pH 7.15. Sprays were provided in brown, light-rejecting glass containers to prevent oxidation of AMB and replaced by freshly prepared solutions at 2-week intervals. Patients were instructed to keep the spray in a refrigerator and to take 2 puffs per nostril 4 times daily. One puff emitted 100 µL solution on average, with droplets of an aerodynamic diameter of 30 to 70 µm, resulting in a total daily dose of 4.8 mg AMB.

### Concomitant therapy and assessment of compliance

Patients were excluded if any antifungal therapy, corticosteroids (topical or systemic), or antihistamines were started <3 weeks before or during the study period. Patients with stable disease under a long-term treatment were allowed to continue their medication as before. All patients were asked for any drug intolerance and were encouraged to continue study medication at regular intervals. At the end of treatment, patients were instructed to return all spray containers and asked for regular study medication intake and any noticed side effects.

### Study design and statistical analysis

A prospective, double-blind, randomized, placebo-controlled parallel group pretest-posttest design was chosen (Fig 1). The response rate, defined as a 50% reduction of the pretreatment CT score, was the primary outcome variable. To increase the sensitivity to subtle changes, a modified Lund and Mackay CT score was applied that classified sinus opacification into 5 stages (Table II). For sample size calculation, a control group response rate of 10% and an active drug response rate of 40% were anticipated. The type I error was set to 0.05 (1-sided), the power to 80%. This resulted in a sample size of 30 patients per group. For an intention-to-treat evaluation, dropouts were to count as nonresponders. To allow a per-protocol evaluation, dropouts were compensated for by recruitment of additional patients.

The response rates of the primary outcome variable in the AMB and control groups were compared with the 1-sided Fisher exact test. Moreover, the score differences of the various outcome parameters before and after treatment in AMB and control groups were compared with the 2-sided Mann-Whitney *U* test.<sup>8</sup> Calculations were performed with SYSTAT 10.2 (Systat Software, Richmond, Calif). All results are expressed as medians ± interquartile ranges. The Department of Biometry and Medical Documentation, University of Ulm, carried out all blinding procedures.

### Allergen skin test and diagnostic nasal lavages

Skin prick tests with inhalant allergens common in Central Europe and to *Aspergillus fumigatus*, *Candida albicans*, *Alternaria alternata*, *Penicillium notatum*, *Cladosporium herbarum*, *Fusarium moniliforme*, *Curvularia lunata*, and *Mucor mucedo* were performed on the forearm of each patient according to the recommendations of the European Academy of Allergy and Clinical Immunology.<sup>9</sup> Standard nasal lavage was performed after mucosal decongestion by using 5 mL sterile isotonic saline per nostril. The fluid samples were kept at 4°C until microbiological examination.

### Fungal cultures and microscopy

To detect fungal elements in nasal lavage specimens, standard culture techniques, fluorescence microscopy, and 2 different PCR assays were used. A patient was considered fungus-positive if at least 1 of these methods could demonstrate fungal elements. All nasal lavage specimens were processed under laminar flow to minimize contamination. A negative control paralleled all processing steps. Results of fungal investigations were considered valid only if these controls were negative. Fungal cultures were performed as described previously.<sup>10</sup>

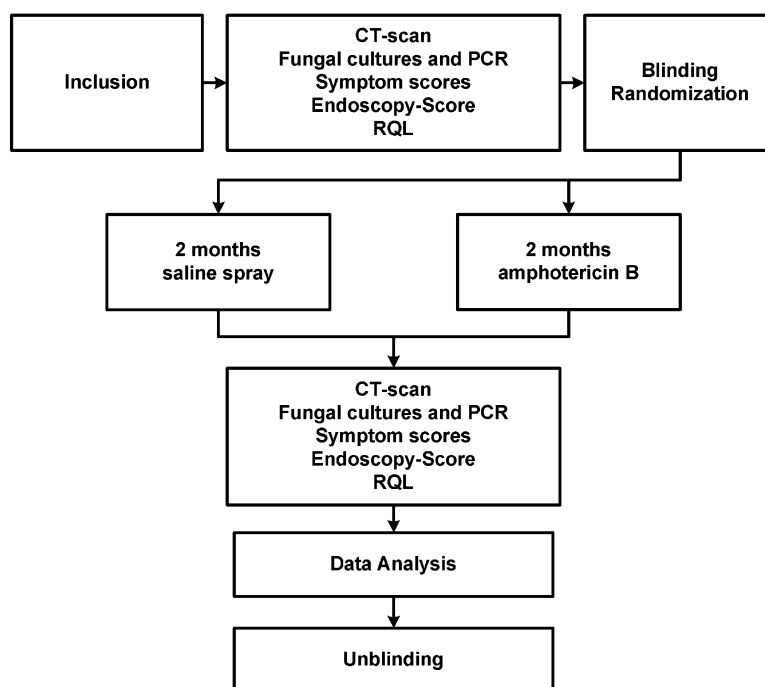


**FIG 1.** Study design. A pretest-posttest double blind control group design was used. Patients were randomly allocated to the 2 treatment arms in this study.

**TABLE II.** CT score (modified after Lund and Mackay<sup>13</sup>) and rhinosinusitis quality of life score (modified after Juniper et al<sup>15</sup>)

| CT score                                                                                                                          | Quality of life score                                                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Each side was separately evaluated for opacification of maxillary, anterior and posterior ethmoidal, sphenoidal and frontal sinus | Subjective estimate on 7-point scale, 0 (not troubled by nose symptoms) to 6 (extremely troubled by nose symptoms) |
| 0 = Not opacified                                                                                                                 | • Regular activities at home and at work?                                                                          |
| 1 = Less than 1/3 opacified                                                                                                       | • Recreational activities?                                                                                         |
| 2 = Between 1/3 and 2/3 opacified                                                                                                 | • Sleep?                                                                                                           |
| 3 = More than 2/3 opacified, but still air-containing                                                                             | • Tiredness and/or fatigue?                                                                                        |
| 4 = Complete opacification (no air)                                                                                               | • Thirst?                                                                                                          |
|                                                                                                                                   | • Feeling irritable?                                                                                               |

## PCR assays

Standard precautions to prevent PCR assay contamination were followed.<sup>11</sup> Sample preparation and technique of *Aspergillus*-specific nested PCR have previously been described.<sup>10</sup> For panfungal PCR, the broad range primers S1 and CUF1 were used, amplifying a 194-bp segment of the 18S rDNA of a wide variety of fungal species.<sup>12</sup> PCR products were subjected to 2% agarose gel electrophoresis, visualized by ethidium bromide staining, and detected under UV light. The amplified fungal DNA was hybridized with the biotinylated oligonucleotide probes V2AS (10 ng/mL; specific for *Aspergillus* and *Penicillium*) and V2CA (50 ng/mL; specific for *Candida*) at 48°C. Hybridization products were detected with the GEN-ETI-K DNA enzyme immunoassay (BykDiaSorin, Düsseldorf, Germany). The sensitivity had been determined at 1 pg *A fumigatus* DNA and 40 *A fumigatus* conidiospores, respectively.<sup>12</sup> Controls for each PCR run included 10 pg and 1 pg *A fumigatus* DNA as positive controls, and 2 negative controls: 1 fully processed DNA-free sample preparation and 1 DNA-free PCR mixture.

## Assessment of outcome parameters

All outcome parameters were assessed before and after an 8-week course of the study medication. Coronal paranasal sinus CT scans in

bone window settings were evaluated according to the scores detailed in Table II.<sup>13</sup> The prestudy CT scans were obtained from the referring physicians. Posttreatment CT scans were performed at the Department for Diagnostic Radiology, University of Ulm, by using a spiral tomograph (SeleCT, Marconi, Israel). Symptom scores were assessed with a modified Lund and Kennedy score system by using 10-cm visual analogue scales.<sup>14</sup> Patients were asked for nasal blockage, facial pain, smell disturbance, nasal discharge, and sneezing. For assessment of RQL (Table II), patients were asked to estimate their impairment during the previous week on a 7-point scale.<sup>15</sup> The values were added to obtain a final score (range, 0-36). Endoscopy scores were assessed according to Malm.<sup>16</sup> After mucosal decongestion, rigid nasal endoscopy was performed. Polyp extension was classified by 1 investigator (M. W.) from 0 (no polyps) to 3 (polyps fill whole nasal cavity) for each side.

## RESULTS

Of 120 screened patients, 78 patients were enrolled. Common reasons for ineligibility were too low CT or symptom scores. Thirty-nine patients were randomly

allocated to each group. There were 15 study withdrawals. The reasons were intolerance of the study medication (6 AMB, 1 control), failure to appear for final examination (3 AMB, 4 control), and discontinuation of study medication because of an acute exacerbation of CRS (1 AMB). Three patients could not be evaluated because of incomplete data, ie, missing CT scan at final examination (2 control) and lack of material for microbiological examinations (1 AMB). In total, 60 patients finished the study per protocol. Twenty-eight were in the AMB group and 32 in the control group. With the exception of sex, demographic and clinical characteristics were similar in both treatment arms (Table III). The patients in the AMB group reported nasal burning ( $P < .005$ ) and nasal blockage ( $P < .05$ ) more frequently than the patients in the control group. Serious adverse events were not observed.

### Detection of fungal elements

Of the 60 patients, 38 demonstrated fungal organisms in nasal lavage before study treatment (17 AMB, 21 control). The most commonly detected fungi were *Aspergillus* spp ( $n = 18$ ) followed by *Penicillium* spp ( $n = 11$ ).

### CT score (primary outcome variable)

Two positive treatment responses were counted in the AMB group. In the control group, no positive response was detected. Neither in the per-protocol analysis ( $n = 60$ ;  $P > .2$ ) nor in the intention-to-treat analysis ( $n = 78$ ;  $P > .2$ ) did this result reach statistical significance. At the start of the study, CT scores were similar in both groups. In the AMB group, the median CT score before treatment (Fig 2) was 29.0 (23.8-33.5); after treatment, it was 26.5 (19.5-35.8). In the control group, it was 28.5 (23.3-32.0) before treatment and 26.5 (23.0-32.0) after treatment. The score differences before and after treatment were similar in the AMB and control groups ( $P > .2$ ).

### Secondary outcome variables

Before treatment, median symptom scores in the AMB group (28; 23.3-31.0) and control group (26.5; 21.3-33.8) did not differ relevantly. After treatment, the median score in the AMB group (26.0; 21.3-29.8) was worse (Fig 3) than in the control group (16.5; 12.0-24.0;  $P < .005$ ). Similarly, pretreatment median scores of RQL in the AMB group (22.5; 17.8-26.0) and control group (20.0; 11.8-23.8) were comparable. After treatment, the median score in the AMB group (20.5; 14.5-26.0) remained almost unaltered, whereas it was lower in the control group (10.0; 4.3-17.8;  $P < .1$ ). The median endoscopy scores were almost identical in the AMB and control groups (4 vs 4) and did not change remarkably after treatment.

The pretest-posttest study design allowed evaluation of the effects of successful fungus elimination. Four constellations were possible: fungal elements were detected before and after the treatment period ( $n = 22$ ), or before the treatment, but not after the treatment ( $n = 16$ ). This particular constellation should have been associated with a positive outcome if the assumptions about fungal elements as the main causative agent of CRS were true.

TABLE III. Demographic and clinical data of patients

|                                  | AMB                 | Control             |
|----------------------------------|---------------------|---------------------|
| Patients, n                      | 28                  | 32                  |
| Age, median                      | 54 y (range, 37-67) | 48 y (range, 25-77) |
| Sex, M/F*                        | 23/5                | 17/15               |
| Positive skin prick test†        | 4 (14%)             | 5 (16%)             |
| Acetylsalicylic acid intolerance | 4 (14%)             | 8 (25%)             |
| Bronchial asthma                 | 8 (29%)             | 8 (25%)             |
| Systemic corticosteroids         | 0                   | 1 (3%)              |
| Corticosteroids nasal            | 12 (43%)            | 12 (38%)            |
| Corticosteroids inhaled          | 5 (18%)             | 3 (9%)              |
| Previous sinus surgery           | 17 (61%)            | 16 (50%)            |

\* $P < .05$ .

†To common inhalant allergens including *A fumigatus*, *C albicans*, *A alternata*, *P notatum*, *C herbarum*, *F moniliforme*, *C lunata*, and *Mucedo*.

Additional constellations included negative fungus detection before and after the treatment period ( $n = 11$ ) and negative detection before but positive detection after the treatment period ( $n = 11$ ). The influence of these constellations on the outcome parameters was evaluated with the Kruskal-Wallis test. The state of fungus positivity had no effect on the CT scores, the symptom scores, the RQL scores, or the endoscopy scores (all  $P$  values  $> .2$ ).

### DISCUSSION

Fungal infection may cause severe acute and chronic sinusitis in the immunocompromised host,<sup>17</sup> whereas fungal elements are regarded frequent innocent bystanders in cultures obtained from the respiratory tract in immunocompetent hosts.<sup>18</sup> AFRS is a well defined entity of CRS and is regarded as an IgE-mediated hypersensitivity reaction to fungal colonization of the paranasal sinus mucosa. Recently, a fungal etiology has been postulated in more than 90% of patients with CRS with or without nasal polyps.<sup>1</sup> According to this concept, ubiquitous fungi become entrapped in sinonasal mucus and are attacked by eosinophils, resulting in secondary mucosal inflammation.

If fungal elements are the main cause of CRS, fungal eradication should improve the course of the disease. Systemic antifungal treatment of AFRS yielded inconclusive results and may cause severe adverse effects.<sup>19,20</sup> In 2 studies on topical antifungal treatment of CRS in immunocompetent hosts, beneficial effects were reported.<sup>2,3</sup> However, both studies were uncontrolled and thus susceptible to observer bias.<sup>4</sup> Furthermore, the antifungal agent was administered as a nasal lavage, which itself is an effective treatment of CRS.<sup>5,21</sup> Therefore, these studies could not convincingly demonstrate benefits of nasal antifungal treatment. To evaluate the effect of nasally administered AMB on disease severity in patients with severe CRS, a placebo-controlled, double-blind study was conducted.

Study participants were recruited from patients with CRS referred for paranasal sinus surgery to a tertiary

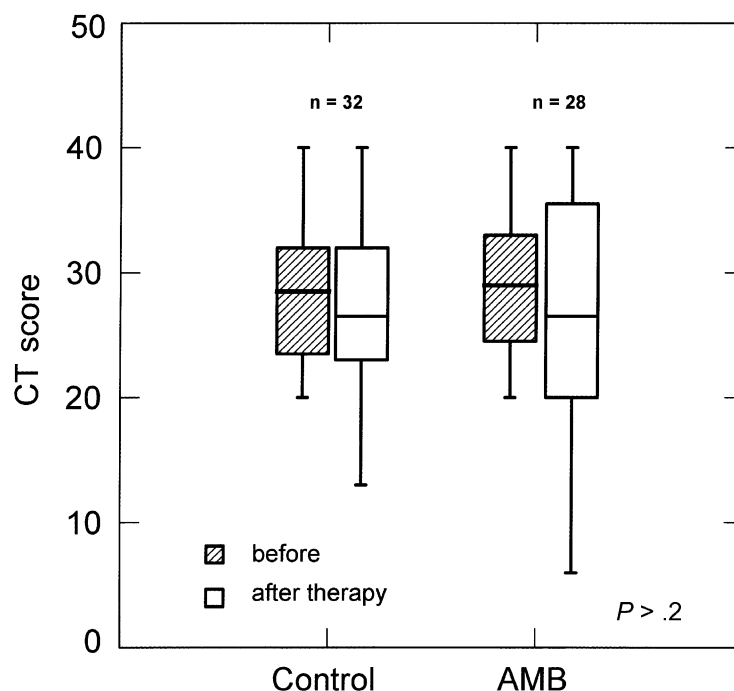


**FIG 2.** CT scores (line in box, median; box, interquartile range; whiskers, lower and upper extremes) before and after 8 weeks of treatment with saline (control) or AMB nasal spray.

surgical center. This implies selection of patients with long-standing disease refractory to common medical therapy. In addition, patients had to exceed a minimum CT score, symptom score, and endoscopy score for inclusion, resulting in a homogenous study group of patients with severe CRS. Sufficiently high initial scores should also allow to detect treatment-related improvements. Patients with a history indicating an impaired systemic immune response or with suspected or proven AFRS as defined by the Bent and Kuhn<sup>7</sup> criteria were excluded. Thus, the results of this study cannot be extrapolated to patients with less severe sinusitis,<sup>2</sup> immunocompromised patients in whom beneficial effects of nasal AMB therapy have been described,<sup>22</sup> or patients with AFRS.

Amphotericin B seemed an appropriate drug because it is active against the most frequently identified molds within the paranasal sinuses, such as *Aspergillus* spp. and *Penicillium* spp. Moreover, fractions involuntarily swallowed are not absorbed. Thus, only minor systemic adverse effects were expected. To avoid confounding effects of nasal lavages, AMB was applied as a nasal spray. The applied concentration of 3 mg/mL is approximately 1000 to 3 000 times higher than the minimum inhibitory concentrations for relevant fungi.<sup>23</sup> The application volume of 200  $\mu$ L per side is the maximum volume that can be applied without relevant nasopharyngeal overspill.<sup>24</sup> It is assumed that with this application mode, mucosal surfaces exposed to the nasal air stream and the nasal mucus transport routes were reached. However, neither nasal sprays nor nasal lavages

are supposed to access the sinus lumen in substantial amounts.

A pretest-posttest control group design was chosen for this double-blind, placebo-controlled parallel group trial. Patients were randomly allocated to the 2 treatment arms by the Department of Biometry and Medical Documentation, University of Ulm. To assess outcome, we used the CT score, because it was assumed that this parameter was least influenced by observer bias. A previous sample size determination was performed on the basis of the supposed proportions of a positive outcome in the 2 treatment arms. Demographic and clinical characteristics were similarly distributed in both treatment arms, except sex (Table III). The lower relative frequency of female subjects in the AMB group was an unfavorable result of the randomization process. However, examining 9 population characteristics, the chance for 1 uneven distribution at the 5% level is approximately 37%. To the best of our knowledge, there is no evidence that sex influences the effectiveness of sinusitis therapy or antifungal treatment. Thus, the uneven sex distribution is not supposed to bias the results of this study. AMB irritates the nasal mucosa. To assure blinding of investigators, the mild irritant chinin sulfate was added to the control spray. Neither patients nor investigators were aware of the kind of treatment during the entire study period.

Disease severity was measured with 4 widely accepted score systems, ie, a modified CT score developed by Lund and Mackay,<sup>13</sup> a modified rhinosinusitis symptom score by Lund and Kennedy,<sup>14</sup> a rhinosinusitis quality of life

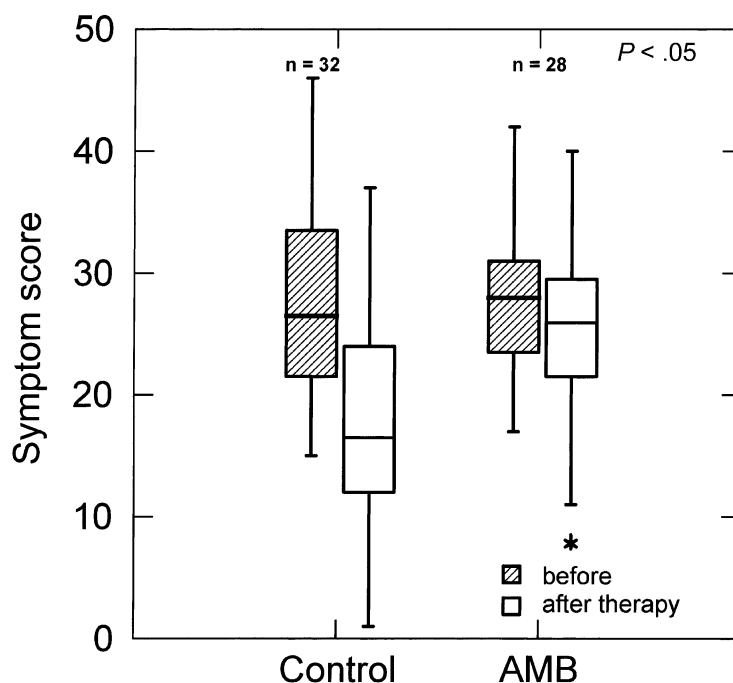


**FIG 3.** Symptom scores (line in box, median; box, interquartile range; whiskers, highest and lowest values excluding outliers; asterisks, outliers) before and after 8 weeks of treatment with saline (control) or AMB nasal spray.

score modified after Juniper et al,<sup>15</sup> and an endoscopy score for nasal polyps developed by Malm.<sup>16</sup> Ethical problems arose with the control CT at the end of the study. Therefore, a low-radiation CT setup without contrast media was used, which allowed reduction of radiation dose by 75% compared with standard CT scans. However, with these settings, a reliable differentiation between bone, air, and soft tissues or secretions was feasible. Therefore, a relevant bias caused by different pretreatment and posttreatment CT settings is not assumed.

Three methods for fungal detection have been used: a rapid microscopic screening technique using an optical brightener, standard culture techniques, and PCR techniques with several fungal primers.<sup>10,12</sup> Nasal lavages were pretreated with the mucolytic agent dithiothreitol to make fungal elements accessible for diagnostic detection.<sup>1</sup> Various measures were met to identify and avoid sample contamination, including a sterile laboratory control paralleling the patient specimen during all preparative steps. Fungal elements were detected in 38 of 60 (63%) of the patients before treatment. The fungal detection rates were higher than those reported in other studies in immunocompetent patients with CRS lacking typical clinical signs of fungal disease.<sup>25,26</sup> The higher detection rate may be explained by an additive effect of the various sensitive methods used. In contrast, cultural detection of fungi in approximately 90% of patients with CRS has been reported recently.<sup>1,27</sup> The reasons for the high detection rates obtained in these studies are unclear. Among other factors, geographic variations,<sup>28</sup> fungal contamination of the air in hospital rooms<sup>29</sup> inhaled by the patients before

the investigation, or laboratory sample contamination may be involved.

Consistently, in none of the investigated outcome variables was a relevant improvement observed (all  $P$  values  $>.2$ ). It is thus assumed that patients with CRS do not benefit from nasal AMB treatment. In comparison with the control group, the posttreatment symptom scores were distinctly worse in the active drug arm ( $P < .005$ ). Moreover, 6 patients from the active drug group, compared with 1 patient in the control group, withdrew from the study because of nasal symptoms. The microbiological tests at the start and the end of the study allowed identification of a subgroup of patients in whom fungal elements had been detected before but not after the treatment period. In these patients, the hypothetical therapeutic aim, ie, eradication of fungus, had actually been achieved. If the underlying hypothesis was true, these patients should have improved. This was not the case ( $P > .2$ ).

In conclusion, the disadvantages of nasal AMB therapy outweighed the benefits. In consequence, the authors currently cannot see any indication for nasal AMB treatment in patients with severe CRS. Moreover, the results of this study cast the assumption of fungal elements as essential causative agents of CRS into severe doubt. They belong rather to the physiologic flora of the upper respiratory tract and are considered innocent bystanders.

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