A RANDOMIZED, DOUBLE-BLIND TRIAL OF NYSTATIN THERAPY FOR THE CANDIDIASIS HYPERSENSITIVITY SYNDROME

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Abstract Background. Candida albicans infection has been proposed to cause a chronic hypersensitivity syndrome characterized by fatigue, premenstrual tension, gastrointestinal symptoms, and depression. Long-term antifungal therapy has been advocated as treatment for the syndrome, which is most often diagnosed in women with persistent or recurrent candida vaginitis.

Methods. To determine the efficacy of nystatin therapy for presumed candidiasis hypersensitivity syndrome, we conducted a 32-week randomized, double-blind, crossover study using four different combinations of nystatin or placebo given orally or vaginally in 42 premenopausal women who met preset criteria for the syndrome and had a history of candida vaginitis. The outcomes studied were the changes from baseline in scores for vaginal, systemic, and overall symptoms and in the results of standardized psychological tests.

Results. The three active-treatment regimens (oral and vaginal nystatin, oral nystatin and vaginal placebo, and oral placebo and vaginal nystatin) and the all-placebo regimen significantly reduced both vaginal and systemic symptoms (P<0.001), but nystatin did not reduce the systemic symptoms significantly more than placebo. On average, the scores for systemic symptoms improved 25 percent with the three active-treatment regimens and 23 percent with the all-placebo regimen, a difference of only 2 percent (95 percent confidence interval, -3 to 7 percent). As expected, the three active-treatment regimens were more effective than placebo in relieving vaginal symptoms (P<0.001). All four regimens reduced psychological symptoms and global indices of distress; there were no significant differences among the treatment regimens.

Conclusions. In women with presumed candidiasis hypersensitivity syndrome, nystatin does not reduce systemic or psychological symptoms significantly more than placebo. Consequently, the empirical recommendation of long-term nystatin therapy for such women appears to be unwarranted. (N Engl J Med 1990; 323:1717-23.)

In recent years Candida albicans, a yeast that is part of the normal human intestinal flora, has been thought by some to cause a disorder variously known as the candidiasis hypersensitivity syndrome, chronic candidiasis, candida-related complex, and the “yeast connection.”1-3 According to Truss and Crook,1,2 the primary proponents of this hypothesis, the syndrome is caused by an overgrowth of C. albicans on mucous membranes and in the gastrointestinal tract in response to several factors, including the use of broad-spectrum antibiotics or oral contraceptives and pregnancy. This overgrowth of C. albicans results in inflammation and invasion of mucous membranes, with attendant local symptoms and, the proponents maintain, an allergic or toxic generalized response. Most women who are given the diagnosis of the candidiasis hypersensitivity syndrome have recurrent or persistent candida vaginitis or other mucocutaneous candida infections, in addition to severe premenstrual tension and menstrual irregularity. Chronic gastrointestinal symptoms, such as bloating, heartburn, constipation, and diarrhea, as well as central nervous system manifestations, including severe depression or anxiety, loss of ability to concentrate, and memory deficits, are also common. Other frequently described symptoms include fatigue, irritability, headache, and nagging respiratory symptoms such as persistent nasal congestion. The candidiasis hypersensitivity syndrome, along with chronic mononucleosis due to infection with the Epstein-Barr virus, chronic brucellosis, hypoglycemia, fibrositis, and environmental allergy syndrome, has been offered as a potential cause or explanation of the chronic fatigue syndrome.4-6

The candidiasis hypersensitivity syndrome is usually identified on the basis of a patient’s clinical presentation alone; in general, laboratory tests are not helpful, although allergy testing is often used. Only

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Supported by the Critical Illness Research Foundation, Birmingham, Ala.; a General Clinical Research Center grant (RR00032) from the National Institutes of Health; and a contract (NO1AI-52562) with the National Institute of Allergy and Infectious Diseases.
recently has a controlled study been undertaken to evaluate diagnostic criteria. Patients are given long-term therapy with oral (and often vaginal) nystatin, which is usually administered in increasing doses until the symptoms are relieved. In addition, patients are instructed to avoid broad-spectrum antibiotics, corticosteroids, oral contraceptives, and diets high in carbohydrates. Advocates claim that many patients respond dramatically to such therapy. Experience has been anecdotal thus far, however, and no objective, prospective, and blinded studies have addressed the true effect of nystatin or other antifungal agents on patients thought to have the syndrome. Accordingly, we conducted a randomized, double-blind, crossover study of treatment with oral and vaginal nystatin as compared with placebo in 42 premenopausal women with presumed candidiasis hypersensitivity syndrome.

METHODS

Criteria for Enrollment

Enrollment was limited to premenopausal women from 21 through 40 years of age with a history of candida vaginitis that had been aggravated by antibiotic therapy and had responded to nystatin or other local antifungal agents. The women were required to have three of the following five additional clinical features thought to be especially common in patients with the candidiasis hypersensitivity syndrome: gastrointestinal symptoms of unknown cause lasting for at least one year, upper or lower respiratory tract symptoms suggesting respiratory allergy, symptoms of premenstrual distress, moderate-to-severe depression without vegetative or psychotic features, and difficulty with short-term memory or concentration. Patients were excluded if they were pregnant at the time of entry into the study; if they were receiving oral contraceptive, estrogen, or progestosterone therapy; if they were taking corticosteroids, other immunosuppressive agents, or nonsteroidal antiinflammatory agents; if they were receiving concomitant antibiotic therapy (or if antibiotics were administered for more than 21 consecutive days during the study); if they had evidence of invasive candidal disease, including esophagitis; if they had a history of diabetes mellitus, gastrectomy, major bowel surgery, alcoholism, drug addiction, or any known immunocompromising condition; or if they were allergic to tartrazine, the dye in the placebo. Written informed consent was obtained from each patient.

Treatment Regimens

During the 32 weeks of the study, each patient followed four different treatment regimens (A, B, C, and D), consisting of the four possible combinations of oral nystatin or placebo with vaginal nystatin or placebo. As shown in Table 1, the patients followed each regimen for an eight-week period. With the use of a Latin-square design, the patients were randomly assigned to one of four sequences in which the four treatment regimens were administered during the 32 weeks: A B C D (sequence 1), B D A C (sequence 2), C A D B (sequence 3), and D C B A (sequence 4). The study was double-blinded, and the individual treatment codes were not broken until all the patients had completed therapy.

Nystatin powder was packaged in gelatin capsules for oral and intravaginal use. The placebo consisted of starch in powder form, colored with minute amounts of tartrazine to give it an appearance identical to that of the nystatin capsules. Sampling by blinded observers revealed no marked differences in taste between the two types of oral capsules. The patients, who were instructed to swallow the oral capsules unopened and with a liquid, ingested one capsule (containing 500,000 units of nystatin or 200 mg of starch) four times daily during the first two weeks of each treatment block. The vaginal capsules (containing 100,000 units of nystatin or 150 mg of starch) were inserted once daily by the patients with the use of applicators. The patients doubled the dose of oral capsules twice during each treatment block, after two and four weeks. Thus, from the fifth through the eighth week of each block, the patients were taking 16 oral capsules daily (8 million units of nystatin or 3.2 g of starch). In each successive eight-week block, through the end of week 32, the patients repeated the cycle with another treatment regimen.

Evaluation before, during, and on Completion of Therapy

Upon entry into the study, at weeks 2 and 4, and every four weeks thereafter, the patients filled out questionnaires listing 18 different symptoms (Table 2). On the basis of the patients' responses, the symptoms were classified as being absent, mild, moderate, or severe. Improvement in individual symptoms was noted on the basis of a decline in the severity grade — e.g., from severe to mild. The overall symptom score consisted of the sum of the severity grades for all 18 symptoms, whereas the vaginal-symptom score and the systemic-symptom score consisted of the sum of the severity grades for the 3 vaginal symptoms and the 15 systemic (nonvaginal) symptoms, respectively.

The patients were also examined at four-week intervals for six physical findings: oral thrush, genital or perianal rash, wheezing, nasal mucosal edema, abdominal tenderness, and abnormal vaginal discharge. The findings were recorded as absent, mild, moderate, or severe, and both individual and overall scores were assigned. A pelvic examination, including vaginal and rectal swabbing for fungal cultures, was performed on entry into the study, at eight-week intervals, and more frequently as indicated. Both selective (Mycol) and enriched (Sabouraud dextrose) mediums were inoculated, and the semiquantitative growth of fungi was determined.

A multidimensional inventory of symptoms reported by the patient, called the SCL-90-R, was administered on entry and at the end of each eight-week block, to assess more objectively the presence of depression and other forms of symptomatic psychological stress and to measure three global indexes of distress. Memory functions (immediate recall, attention, and concentration) were also monitored at the same intervals with a digit-span test. A modified intelligence test was used initially to control for the influence of intelligence on memory functioning. At the end of each treatment block, the patients were asked to guess which oral and vaginal agents they had most recently received. To assess compliance, pills were counted at each visit. In addition, the patients were questioned about the concurrent use of other medications.

Study Design and Statistical Analysis

Our objective was to determine whether there was sufficient evidence to suggest that nystatin given orally, vaginally, or by both routes was superior to placebo. To detect a difference of 1.5 SD between any two regimens with a significance level (Type I error) of 0.05 and a power (1 - Type II error) of 0.80, a minimum of eight patients was required for each of the four treatment se-
Table 2. Analysis of Individual Symptoms after Adjustment for Symptom Score at the Start of Each Treatment Block.

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>REGIMENS COMPARED (P VALUES)</th>
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<tr>
<td></td>
<td>A VS. D</td>
<td>AB VS. CD</td>
<td>ABC VS. D</td>
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<td>Vaginal</td>
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<td>Pruritus</td>
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<td>Burning</td>
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<td>Abnormal discharge</td>
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<td>Systemic</td>
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<td>Abdominal bloating</td>
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<td>Abdominal pain or cramping</td>
<td>0.049</td>
<td>0.045</td>
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<td>Nausea or indigestion</td>
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<td>Diarrhea</td>
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<td>Constipation</td>
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<td>Perianal pruritus</td>
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<td>Menstrual irregularity</td>
<td>0.005</td>
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<td>Premenstrual distress</td>
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<td>Decreased short-term memory</td>
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<td>Poor concentration</td>
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<td>Depression</td>
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<td>Lethargy</td>
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<td>Rhinitis</td>
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<td>Sneezing</td>
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<td>Wheezing</td>
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*Only P values ≤0.05 are shown. Values were obtained by analysis of covariance. A denotes oral nystatin plus vaginal nystatin, B oral nystatin plus vaginal placebo, C oral placebo plus vaginal nystatin, and D oral placebo plus vaginal placebo.

sequences. Thus, a minimum of 32 patients who could be evaluated was needed.

The data management and statistical analyses were supported by CLINFO and the Statistical Analysis System. All the statistical tests were two-tailed at the 0.05 significance level. Analysis-of-covariance techniques were used to compare the effects of the four treatment regimens on the following outcomes: proportion changes from the values at base line (week 0) in the three symptom scores, the scores for individual symptoms, and the psychological measures. Treatments were compared after adjustment for eight-week treatment blocks, sequences, variability among patients, and carryover effects of the preceding treatment block. The method of linear contrasts was used to compare the following treatment regimens: A with D, AB with CD, and ABC with D. The overall difference between drug and placebo in their effects on the systemic symptom score was estimated as the linear contrast of ABC versus D, and the 95 percent confidence interval was estimated from the standard error of the contrast. The effectiveness of each regimen in reducing the symptom scores was assessed by a t-test of the adjusted means. To assess the possibility of a placebo effect during the first two weeks of therapy, each of the active-treatment regimens was compared with the placebo regimen by the method of linear contrasts. Physical findings and digit-span test results were analyzed to a more limited degree, including proportional changes from base line.

The four sequences (1, 2, 3, and 4) were divided into two broader dosage groups for post hoc analysis of the effects of treatment on systemic symptoms and the global severity index, the best single indicator of psychological distress. The patients randomly assigned to either sequence 1 or sequence 3 were combined, because these patients followed the double-drug regimen (regimen A) during one of the first two treatment blocks (the first 16 weeks of the study) and followed the double-placebo regimen (regimen D) during one of the last two treatment blocks (the second 16 weeks of the study). Similarly, the patients randomly assigned to either sequence 2 or sequence 4 were combined, because these patients followed the double-placebo regimen during 8 of the first 16 weeks and the double-drug regimen during 8 of the second 16 weeks. An analysis-of-variance methods for repeated measures were used to compare the "double-drug" and "double-placebo" groups with respect to the proportional changes in systemic-symptom score from week 2 to weeks 4, 8, 12, and 16 and from week 16 to weeks 20, 24, 28, and 32, and the proportional changes in the global severity index from week 0 to weeks 8 and 16 and from week 16 to weeks 24 and 32.

**RESULTS**

**Study Population**

Fifty patients were enrolled in the study. Eight of these withdrew before the end of the first eight-week treatment block and were excluded from the analysis: two from sequence 1 and three each from sequences 2 and 4. Thus, 42 patients (mean age, 32) could be evaluated. Two of these withdrew early because of pregnancy, but they were included in the analysis because they had completed at least one eight-week treatment block. One withdrew from sequence 2 after 16 weeks of therapy, and the other withdrew from sequence 4 after 8 weeks of therapy. The number of patients who completed a given treatment regimen during each treatment block is shown in Table 1. Thirteen patients included in the group who could be evaluated received systemic antimicrobial agents for periods of 1 to 14 days after beginning the study. These 13 patients were distributed among the four treatment sequences as follows: 3 in sequence 1, 4 each in sequences 2 and 3, and 2 in sequence 4.

**Outcomes**

The effects of the treatment regimens on the proportional change from base line in the vaginal, systemic, and overall symptom scores are shown in Figure 1. The three active-treatment regimens and the all-placebo regimen reduced vaginal symptoms significantly (P<0.001). Moreover, all the comparisons of vaginal-symptom scores among the treatment regimens were statistically significant (A vs. D, P<0.001; AB vs. CD, P = 0.018; and ABC vs. D, P<0.001). There were also significant differences in the proportional improvement in vaginal-symptom score between treatment blocks (P<0.001) and between patients (P<0.001). Significant carryover effects of treatment on the vaginal-symptom score were detected (P = 0.033), suggesting that the benefit of nystatin persisted after patients were switched to placebo. This effect is most clearly seen in the patients in sequence 1, who received the three active regimens (A, B, and C) followed by the placebo regimen (D).

By contrast, no statistically significant treatment differences or carryover effects were detected for the proportional change in systemic symptoms (Fig. 1). Although all four treatment regimens, including the double-placebo regimen, reduced nonvaginal symptoms significantly (P<0.001), the active regimens were no more effective than the placebo regimen. The only factor shown to influence the systemic-symptom score was variability among patients (P<0.001). When the results for the active-drug regimens (ABC) were combined, the mean proportional improvement in systemic-symptom score was 25 percent. By contrast, the mean proportional improvement in the systemic-symptom score for the placebo regimen was 23 percent, yielding an overall difference between drug
and placebo of 2±5 percent (95 percent confidence interval, −3 to 7 percent).

All four treatment regimens had a positive effect on overall symptoms. Significant differences were noted only between regimens A and D (the all-nystatin regimen and the all-placebo regimen; P = 0.013) (Fig. 1). The effects of regimens A and D on the overall symptom score can be further understood by an evaluation of individual symptoms (Table 2). Significant differences between the two regimens were found for each of the three vaginal symptoms and for four of the systemic symptoms. The strikingly positive effect of the all-nystatin regimen on vaginal symptoms and its positive effect on some systemic symptoms explain the significant benefit of this regimen on the overall symptom score. There were significant carryover effects of all the regimens on the overall symptom score (P = 0.038), probably reflecting the positive carryover effects on vaginal symptoms, as described above. Variability among patients was the only other significant factor affecting the overall symptom score (P<0.001). No significant differences among treatments were detected in the proportional changes from base line in the overall scores for the six physical findings.

The question of a possible placebo effect during the initial phase of the study is addressed in Figure 2. Although all the treatment regimens including placebo were associated with proportional improvement in vaginal, systemic, and overall symptom scores from base line to week 2, there were no significant differences between the three active-treatment regimens (A, B, and C) and the placebo regimen (D). That is, during the first two weeks of the study, the three active-treatment regimens did not have a beneficial effect beyond that of placebo. From week 2 to week 8, the placebo regimen exerted no appreciable further benefit, whereas regimen A, the all-nystatin regimen, exerted a progressively beneficial effect on all three symptom scores.

The three active-treatment regimens and the placebo regimen had significant effects on all the psychological symptoms and global indexes of distress measured by SCL-90-R testing, with one exception. The decline in obsessive–compulsive symptoms in the patients following regimen C (oral placebo and vaginal nystatin) did not reach statistical significance. The only difference noted between treatment regimens was that between the oral-nystatin regimens (A and B) and the oral-placebo regimens (C and D) in their effect on somatization or distress arising from perceptions of bodily functions (P = 0.04). Significant differences between treatments were also detected with respect to the proportional change in digit-span scores (A vs. D, P = 0.019; ABC vs. D, P = 0.008). The differences were in the wrong direction, however, since the three active-treatment regimens exerted a negative influence on digit-span scores.

**Analysis of Systemic-Symptom Score and Global Severity Index**

When the four sequences were partitioned into the double-drug and double-placebo groups (see Methods), there was no significant difference between the groups (P = 0.115) with respect to proportional changes in systemic symptoms from week 2 to weeks 4, 8, 12, and 16 (Fig. 3A). In addition, the global severity index declined by 6 percent in the double-drug group and by 9 percent in the double-placebo group, a difference that was not statistically significant (P = 0.404).

Figure 3B shows the proportional change in the systemic-symptom score from week 16 to weeks 20, 24, 28, and 32. Although there was a discernible difference between the effects of the double-drug group and those of the double-placebo group, this difference was
not statistically significant (P = 0.06). Likewise, there was no significant effect on the global severity index, which declined by 6 percent in the double-drug group and increased by 1 percent in the double-placebo group (P = 0.271).

Other Findings

Only 14 percent of the women had positive vaginal cultures for yeast, and only 12 percent had positive rectal cultures on entry into the study. During the study, the incidence of positive vaginal and rectal cultures at the end of each treatment block did not change significantly, ranging from 8 to 12.5 percent (vaginal cultures) and 7 to 10 percent (rectal cultures). Partly because of the low incidence of positive cultures on entry and the minimal changes during the study, no significant differences in the effects of treatment on the culture results were detected.

The proportion of patients who identified their oral medication correctly appeared to increase with time, as follows: block 1, 43 percent; block 2, 49 percent; block 3, 67 percent; and block 4, 61 percent. The corresponding proportions of patients who correctly identified their vaginal medication were 48, 69, 56, and 50 percent.

Discussion

As expected, nystatin therapy reduced vaginal symptoms significantly; each of the treatment regimens containing nystatin was more effective than placebo. The most pronounced benefit was from regimen A, containing both oral and vaginal nystatin (P<0.001). Most important, with regard to the question of the efficacy of nystatin therapy for systemic symptoms in patients with presumed candidiasis hypersensitivity syndrome, our data did not support any clear-cut benefit. The regimens containing nystatin did not significantly reduce systemic symptoms more than the all-placebo regimen did. The only nystatin-containing regimen that exerted any appreciable influence on systemic symptoms was regimen A, and its benefit was significant for only 4 of the 15 systemic symptoms (Table 2). The lack of significant differences between treatments with respect to psychological or cognitive symptoms was reinforced by the results of psychometric and memory testing. Likewise, the overall scores for the six physical findings were not affected by the differences between treatment regimens.

We were concerned that a previous regimen might alter a patient's response to her subsequent regimen. Although the carryover effects of a previous active-treatment regimen (A, B, or C) were shown to have a significant effect on vaginal symptoms, there was no evidence of such an effect on systemic symptoms. The only exception was in the patients in sequence 1 (those assigned to three active regimens followed by placebo). The symptom scores for these patients did not worsen during the final eight weeks of therapy — a finding consistent with either a carryover effect or a benefit from placebo.

The effect of placebo was most cleanly evaluated in the analyses of the first block of treatment, corresponding to weeks 1 to 8. Substantial reductions in systemic symptoms were observed during the first two weeks of therapy regardless of treatment regimen, suggesting a positive placebo effect (Fig. 2). After the first two weeks of therapy and through week 8, an overall placebo effect on systemic symptoms appeared to persist but not increase. However, consistent linear trends in systemic-symptom score among the patients taking placebo in each subsequent treatment block were not observed. The inability of many patients to identify the specific study drugs correctly also suggests that a placebo effect had a role in the overall outcome. On the other hand, although systemic symptoms clearly improved in the patients who were following the placebo regimen, it is possible that this improvement represented no more than regression to the mean. In addition, we acknowledge that the ability of a study patient to identify a drug correctly was in-
fluenced by her perceived response to the treatment regimen.

In our attempt to assess the efficacy of nystatin therapy thoroughly, we carried out several post hoc analyses. Data from one such analysis, in which the patients were combined into two broad dosage groups, a double-drug group and a double-placebo group, suggested some benefit for systemic symptoms. Double-drug treatment had a beneficial, although not statistically significant, effect on systemic symptoms during the last 16 weeks of the study (P = 0.06). However, double-drug treatment did not significantly alter the systemic-symptom score in the first half of the study (P = 0.115). Why the double-drug regimen appeared more effective during the second half of the study than during the first half is unclear, unless the explanation relates at least in part to the placebo effect observed during the first two weeks of treatment. In any case, these more positive results must be interpreted cautiously in the light of our other data, which argue strongly against a therapeautic benefit of nystatin in patients with candidiasis hypersensitivity syndrome.

The gastrointestinal tract has been implicated as the reservoir of candida that is responsible for both the syndrome of recurrent vulvovaginal candidiasis and the candidiasis hypersensitivity syndrome. Like other investigators, however, we could not find a significant association between the positive cultures for candida from vaginal sources and those from rectal sources. Moreover, we recovered candida from the vagina in no more than 14 percent of the patients during any block of treatment, and from the rectum in no more than 12 percent, although it is possible that a substantial number of the cultures may have been falsely negative for reasons related to sampling or method. In our study, there was no correlation between positive cultures for candida and systemic symptoms.

Proponents of the existence of the candidiasis hypersensitivity syndrome urge that the avoidance of foods containing yeast or mold and the reduction of dietary carbohydrates are essential components of therapy. Accordingly, the argument can be made that the differences between treatment regimens in our study population might have been more significant if low-carbohydrate or yeast-free diets had been incorporated into the study design. Because any attempt to regulate and monitor the eating patterns of the patients in an outpatient study would have added greatly to an already highly complex study design, we chose not to include diet as a variable. Similarly, we did not include immunotherapy with allergenic extracts of *C. albicans* as part of our treatment regimen.

The existence of the candidiasis hypersensitivity syndrome as a distinct clinical syndrome has been challenged. In 1986, in a position paper, the American Academy of Allergy and Immunology stated that the concept was "speculative and unproven" and that "the diagnosis, the special laboratory tests, and the special aspects of treatment should be considered experimental and reserved for use with informed consent in appropriate controlled trials. . . ." In 1989, investigators at the University of Connecticut prospectively evaluated 100 consecutive adults with a condition the patients themselves had identified as chronic fatigue syndrome. Eight of the 100 believed that their chronic fatigue was associated with a chronic yeast infection, and 92 did not. There were no differences in the medical histories, physical and laboratory findings, or psychiatric evaluations of the two groups of patients, leading the investigators to conclude that they were unable to identify findings specific for the candidiasis hypersensitivity syndrome. Given the dearth of controlled data on various aspects of this syndrome — including its pathogenesis, diagnostic criteria, and response to therapy — controversy and skepticism persist. The negative results of our prospective blinded study of nystatin therapy provide additional objective evidence that the syndrome is not a verifiable condition.

In summary, in the treatment regimens employed, nystatin did not significantly alter the systemic symptoms attributed to the candidiasis hypersensitivity syndrome. As expected, nystatin therapy improved vaginal symptoms significantly, regardless of the route of administration. One possible criticism of our study relates to our focus on only one aspect of therapy — the efficacy of the antifungal drug nystatin. Our study design did not address other therapeutic approaches that have been advocated, including special diets, measures to control the environment, or immunotherapy. Although further controlled studies are needed to address both diagnostic criteria and therapy, our findings do not support the empirical recommendation of long-term nystatin treatment for patients with presumed candidiasis hypersensitivity syndrome.

We are indebted to Ms. Faye Reamies, Ms. Laura Taylor, and Ms. Paula Heath for assistance in the preparation of the manuscript, and to Dr. Seng-jaw Soong and Dr. William Huster for helpful guidance and criticism relating to biostatistical issues.

**References**


INCREASED INCIDENCE OF LYMPHOPROLIFERATIVE DISORDER AFTER IMMUNOSUPPRESSION WITH THE MONOCLONAL ANTIBODY OKT3 IN CARDIAC-TRANSPLANT RECIPIENTS

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Abstract Background. A sudden increase in the incidence of post-transplantation lymphoproliferative disorder among the patients in our cardiac-transplantation program was temporally related to introduction of the immunosuppressive drug OKT3. This monoclonal antibody has come to be widely used in recent years both to prevent and to treat rejection after cardiac transplantation.

Methods. In order to identify variables that predict the development of post-transplantation lymphoproliferative disorder, we analyzed retrospectively a series of 154 consecutive cardiac-transplant recipients at a single institution. Univariate analyses and multivariate analysis by logistic regression were performed.

Results. Among 75 patients who did not receive OKT3, post-transplantation lymphoproliferative disorder developed in 1 (1.3 percent), as compared with 9 of 79 patients who received the drug (11.4 percent); the incidence among the OKT3-treated patients was ninefold higher (odds ratio, 9.5; 95 percent confidence interval, 1.6 to 54.7). According to multivariate analysis, the only factor significantly associated with the development of post-transplantation lymphoproliferative disorder was the use of OKT3 (P = 0.001). A significant increase in risk with increasing doses was also apparent: 4 of 65 patients who received a cumulative dose of 75 mg of OKT3 or less (6.2 percent) had post-transplantation lymphoproliferative disorder, whereas 5 of 14 patients who received more than 75 mg had the disorder (35.7 percent; P < 0.001).

Conclusions. The addition of OKT3 to the immunosuppressive regimen increases the incidence of post-transplantation lymphoproliferative disorder after cardiac transplantation, and the risk increases sharply after cumulative doses greater than 75 mg. We suggest that the risks and benefits of prophylactic OKT3 administration be reassessed in the light of these findings, particularly since the value of prophylactic immunotherapy in cardiac-transplant recipients remains to be clearly established. (N Engl J Med 1990; 323:1723-8.)

POST-TRANSPLANTATION lymphoproliferative disorder is a well-recognized, frequently fatal complication of immunosuppression.¹ ² The term encompasses a spectrum of abnormal proliferations of B lymphocytes that occur after organ transplantation. Such lymphoproliferative disorders have been identified in the wider context of immunodeficiency in general — whether it is congenital, due to human immunodeficiency virus type 1 (HIV), or associated with intensive chemotherapy for leukemia.³ ⁵ The disease has provided insights into the nature of lymphoid cancer and has assumed increasing clinical importance in view of the HIV epidemic and the rising number of organ-transplant recipients. The incidence of post-transplantation lymphoproliferative disorder varies with the organ transplanted; in a large series, Nalesnik et al. reported an incidence of 1 percent for renal transplantation, 1.8 percent for cardiac transplantation, 2.2 percent for liver transplantation, and 4.6 percent for heart–lung transplantation.²

The Epstein–Barr virus (EBV) is believed to have an important role in the pathogenesis of post-transplantation lymphoproliferative disorder. Clinical or serologic evidence of a primary or reactivated EBV infection often precedes the appearance of the disorder.⁶ Tumor tissue has been found to contain EBV DNA, though not in all cases,⁷ and to express viral proteins actively.⁸ The development of post-transplantation lymphoproliferative disorder in immunosuppressed patients is believed to result from inadequate T-cell control over EBV-driven B-cell proliferation.² A histologic spectrum extending from lesions that appear reactive to large-cell non-Hodgkin’s lymphoma has been recognized.³ Both polyclonal and monoclonal proliferations have been identified on the basis of the cell-surface immunoglobulin phenotype.¹ ¹¹ Immunogenotyping by DNA analysis

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