A Survey of Anti-fungal Management in Lung Transplantation

J. Stephen Dummer, MD, a,d Nikoloz Lazariashvilli, MD, a Jean Barnes, RN, ASN, d Mathew Ninan, MD, c,d and Aaron P. Milstone, MD b,d

Background: Fungal infections are an important complication of lung transplantation, but no controlled studies of their management have been performed. Knowledge of actual anti-fungal strategies may aid in the design of future prospective studies.

Methods: Thirty-seven of 69 active lung transplant centers, accounting for 66% of all US lung transplantations, responded to our survey. The survey focused on fungal surveillance, pre- and post-transplant prophylaxis, and approach to fungal colonization.

Results: The median number of lung transplantations performed by the centers in 1999 was 14 per year (range, 1–52), and median time that centers were in in operation was 9 years (range, 2–15 years). Seventy percent of centers had a transplant infectious diseases specialist. Pre-transplant fungal surveillance was performed by 81% of centers, with 67% of these surveying all patients and the remainder surveying only sub-sets of patients. Seventy-two percent of all centers started anti-fungal treatment if Aspergillus spp were isolated before transplantation. Itraconazole was the preferred agent (86%). After transplantation, 76% of centers gave anti-fungal prophylaxis, although 24% of these did so only in selected patients. Prophylactic agents in order of preference were inhaled amphotericin B (61%), itraconazole (46%), parenteral amphotericin formulations (25%), and fluconazole (21%); many centers used more than 1 agent. Prophylaxis was initiated within 24 hours by 71% and within 1 week by all centers. Median duration of prophylaxis was 3 months (range, <1 month–lifetime). All 37 centers used anti-fungal therapy if colonization with Aspergillus spp was detected for a median duration of 4.5 months. Itraconazole was the preferred agent. Only 59% of centers treated patients colonized with Candida spp. In a statistical analysis, centers with larger volumes were less likely to treat pre-transplant colonization with Candida spp but more likely to use agents other than itraconazole for post-transplant colonization with Aspergillus spp. Only 14% of centers engaged in any anti-fungal research at the time of the survey.

Conclusions: The majority of surveyed lung transplant programs actively manage fungal infection with prophylaxis or pre-emptive therapy, despite the absence of controlled trials. This survey may provide an impetus and a basis for designing prospective studies. J Heart Lung Transplant 2004;23:1376-81.

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Invasive fungal infections were recognized as an important complication of heart-lung transplantation shortly after its first clinical successes in 1981.1-3 As the discipline has advanced, bilateral and single lung transplantation have superseded heart-lung transplantation for most indications, but the susceptibility of the transplanted lung to fungal infection and particularly to Aspergillus infection has remained high.4-10 Many lung transplant centers routinely use anti-fungal prophylaxis or are aggressive in treating fungal colonization, but these strategies are based either on observational studies or on best clinical judgement, and no randomized, prospective studies have been performed. Several possible reasons for lack of studies include the small size of most centers, the paucity of funds to support such studies, and ultimately the lack of consensus on what constitutes effective anti-fungal management.

We thought that a systematic survey of current anti-fungal management might provide data that would give an overview of current anti-fungal practices in the United States. In addition, this information would provide a basis and an impetus for developing collaborative studies in the future.

METHODS

In 2001, we offered a survey questionnaire to all 69 active lung transplant programs listed by the United Network for Organ Sharing (UNOS). The Vanderbilt...
University Institutional Review Board approved the survey. The questionnaire was distributed to all transplant programs, and responses could be either paper-based or internet-based. When we needed clarification of results, the medical director was contacted directly.

The survey was divided into 4 main sections, including program demographics, pre-transplant surveillance for fungi, post-transplant prophylaxis for fungi, and post-transplant therapy for fungal colonization. All responses were based on center reporting except for data on program volume, which was extracted from the published 2000 UNOS annual report. We also analyzed responses in relation to the size of the program, the number of years in operation, and the presence or absence of a transplant infectious diseases specialist. We tabulated the data using Excel (Microsoft, Richmond, WA). We used chi-square or Fisher’s exact test to compare categoric values.

RESULTS
Demographics
Thirty-seven (54%) of 69 active lung transplant centers responded to the survey (Appendix I). These 37 programs accounted for 66% of all lung transplant procedures performed in the United States in 1999. The median number of lung transplantations performed in 1999 by the 37 responding centers was 14, with a range of 1 to 52 transplantations per year. Seventy-one (72%) of these centers treated patients who had isolates of *Aspergillus* spp. A variety of agents were used but we noted a strong predilection for itraconazole, which 95% of centers used in at least some colonized patients. Five (24%) of the centers reported use of inhaled amphotericin B, but only 1 center used it exclusively. Only eight (28%) centers did not treat when pre-transplant surveillance cultures revealed *Aspergillus* spp. In contrast with the relatively aggressive response to pre-transplant colonization with *Aspergillus* spp, most lung transplant programs ignored the detection of *Candida* spp before transplantation. Sixty-nine percent of responding programs did not treat patients if pre-transplant culture revealed *Candida*

<table>
<thead>
<tr>
<th>Surveillance and methods</th>
<th>Number of programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum culture only</td>
<td>24 (65)</td>
</tr>
<tr>
<td>Sputum culture and fungal titers</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Fungal titers only</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Bronchoalveolar culture and fungal titers</td>
<td>1 (3)</td>
</tr>
<tr>
<td>No pre-transplant surveillance</td>
<td>7 (19)</td>
</tr>
</tbody>
</table>

### Table 1. Pre-transplant Fungal Surveillance and Methods Used

Table 2 shows data on pre-transplant surveillance for fungal infection. Thirty (81%) of the programs surveyed patients for fungal colonization before surgery. Twenty-four (65%) of the programs used only fungal sputum cultures to evaluate patients before transplantation. Four (11%) of the centers cultured sputum and measured serum titers of anti-fungal antibodies for surveillance. One (3%) of the programs used fungal titers only, and 1 used bronchoscopy with fungal culture of bronchoalveolar fluid as well as serum fungal titers for pre-transplant evaluation. Of the 30 centers that performed pre-transplant surveillance, the majority (67%) surveyed all patient populations (Table 2). The remaining 10 centers surveyed only patients who were thought to be at greater risk of fungal infection. The groups selected for surveillance varied among these centers, but all centers included in their surveillance efforts patients with cystic fibrosis. The frequency of fungal surveillance varied widely. Twelve (40%) of the responders surveyed patients only once, 12 (40%) of the programs surveyed patients more than once, and 4 programs (13%) surveyed patients at intervals of 3 to 6 months. Two (7%) of the programs surveyed patients with cystic fibrosis more than once but surveyed patients with other diagnoses only once.

Table 3 summarizes the actions taken by programs when pre-transplant fungal surveillance cultures revealed *Aspergillus* spp. Only the 29 centers that performed pre-transplant cultures responded to this question. Twenty-one (72%) of these centers treated patients who had isolates of *Aspergillus* spp. A variety of agents were used but we noted a strong predilection for itraconazole, which 95% of centers used in at least some colonized patients. Five (24%) of the centers reported use of inhaled amphotericin B, but only 1 center used it exclusively. Only eight (28%) centers did not treat when pre-transplant surveillance cultures yielded *Aspergillus* spp. In contrast with the relatively aggressive response to pre-transplant colonization with *Aspergillus* spp, most lung transplant programs ignored the detection of *Candida* spp before transplantation. Sixty-nine percent of responding programs did not treat patients if pre-transplant culture revealed *Candida*.
spp. The 9 centers that treated patients with positive Candida culture results also did not have a consistent approach, with 3 using itraconazole, 2 using a topical therapy such as nystatin swish-and-swallow, 1 using fluconazole, and 3 varying the therapy depending on clinical circumstances.

**Post-transplant Prophylaxis for Fungal Infections**

Table 4 presents the use of anti-fungal prophylaxis after transplantation. Twenty-eight (76%) programs performed post-transplant fungal prophylaxis in at least some sub-groups of patients. The most common groups given prophylaxis were patients with cystic fibrosis (70%) and chronic obstructive pulmonary disease (57%). Slightly <50% of the programs gave prophylaxis to patients with bronchiectasis, sarcoidosis, and idiopathic pulmonary fibrosis. The agents used for prophylaxis in order of preference were inhaled amphotericin (61% of centers), itraconazole (48%), intravenous amphotericin, or lipid formulations of amphotericin (25%) and fluconazole (21%). These percentages add up to >100% because a number of centers used >1 agent, either concurrently or sequentially.

Post-transplant prophylaxis was started within 24 hours after transplant surgery in 20 (71%) of the centers, and all centers started prophylaxis within the 1st week. Three centers delayed prophylaxis until >4 days after transplantation. Table 5 shows the duration of fungal prophylaxis. Prophylaxis was continued only during hospitalization in 1 center; the remaining of the programs used prophylaxis for a month or more, with 4 centers continuing anti-fungal medications for the lifetime of the patient. The median duration of prophylaxis was 3 months.

**Formal Bronchoscopic Surveillance After Transplantation**

Thirty-one or 84% of centers performed surveillance bronchoscopy after transplantation at least during the 1st post-transplant year. Of these centers, 24 (65%) performed bronchoscopy at least 4 times in the 1st post-transplant year, and 27 (87%) continued surveillance beyond the 1st year of transplantation.

**Approach to Post-transplant Fungal Colonization**

All responding centers administered anti-fungal therapy to patients in whom Aspergillus was detected either with post-transplant bronchoscopy specimens or sputum cultures in the absence of invasive disease. Seventeen (46%) of the programs reported that they had a routine treatment protocol for post-transplant Aspergillus colonization. The remaining 54% of respondents tailored their treatment individually to the patient’s clinical situation. Figure 1 illustrates the programs’ estimate of how frequently they used amphotericin B and itraconazole for Aspergillus colonization detected after transplantation. As can be seen by the figure, most centers (22; 59%) used itraconazole in >50% of patients colonized with Aspergillus. By contrast, most centers (54%) did not use amphotericin or used it in a small minority of patients. Fifty-eight percent of these centers used an inhaled preparation, whereas the remainder used either parenteral or a combination of parenteral and inhaled amphotericin. The data in Figure 1 show a clear preference for itraconazole in treating post-transplant Aspergillus colonization. The duration of therapy for Aspergillus colonization varied among programs.

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**Table 3. Action Taken When Pre-transplant Surveillance Culture Reveals Aspergillus**

<table>
<thead>
<tr>
<th>Action taken</th>
<th>Number of programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>21 (72)</td>
</tr>
<tr>
<td>Itraconazole only</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Itraconazole and inhaled amphotericin B</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Itraconazole in selected patients</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Inhaled amphotericin B only</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Itraconazole or inhaled amphotericin B</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Itraconazole or Abelcet</td>
<td>1 (3)</td>
</tr>
<tr>
<td>No treatment</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Total</td>
<td>29 (100)</td>
</tr>
</tbody>
</table>

**Table 4. Post-transplant Prophylaxis for Fungal Infection**

<table>
<thead>
<tr>
<th>Post-transplant prophylaxis</th>
<th>Number of programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis performed</td>
<td>28 (76)</td>
</tr>
<tr>
<td>Sub-groups prophylaxed</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>26 (70)</td>
</tr>
<tr>
<td>COPD</td>
<td>21 (57)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>17 (46)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>16 (43)</td>
</tr>
<tr>
<td>IPF</td>
<td>17 (46)</td>
</tr>
<tr>
<td>No prophylaxis performed</td>
<td>9 (24)</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis.

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**Figure 1.** The frequency of use of amphotericin B and itraconazole in treating post-transplant Aspergillus colonization.
Table 5. Duration of Post-transplant Prophylaxis

<table>
<thead>
<tr>
<th>Duration of prophylaxis</th>
<th>Number of programs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During initial hospitalization</td>
<td>1 (4)</td>
</tr>
<tr>
<td>1 month</td>
<td>6 (21)</td>
</tr>
<tr>
<td>2 months</td>
<td>3 (11)</td>
</tr>
<tr>
<td>3 months</td>
<td>6 (21)</td>
</tr>
<tr>
<td>6 months</td>
<td>4 (14)</td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>1 (4)</td>
</tr>
<tr>
<td>12 months</td>
<td>2 (7)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Lifetime</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (100)</td>
</tr>
</tbody>
</table>

(Table 6) with a median of 4.5 months and a range of <1 month to >6 months. One center treated patients until follow-up culture results were negative.

Only three (8%) of the programs had routine treatment protocols for colonization with Candida spp. Nineteen (51%) of the programs tailored treatment to the individual patient, and 15 programs (41%) did not treat Candida colonization in post-transplant patients. Figure 2 shows the frequency of use of 3 anti-fungal medications for treatment of Candida colonization. The responding centers used fluconazole more often than itraconazole and rarely gave amphotericin preparations. The median duration of treatment for Candida colonization was 3 months (range, <1 month->6 months), but 46% of centers gave <1 month of treatment.

Demographics and Anti-fungal Strategies

We analyzed associations between prophylactic and pre-emptive anti-fungal strategies and the size of the centers and their duration of time in operation. Larger programs (≥14 patients per year) were less likely to treat pre-transplant colonization with Candida spp. We also found that larger programs and those in operation for >9 years were more likely to use agents other than itraconazole to treat Aspergillus colonization (p < 0.02). We found no statistically significant association between the availability of a transplant infectious disease expert and any particular anti-fungal strategy. Only 5 centers reported that they had conducted anti-fungal research. All of these studies were industry supported.

DISCUSSION

We think this survey provides a reasonably accurate view of anti-fungal management after lung transplantation because the 37 participating centers accounted for 66% of all lung transplantations performed in the United States. Also, 7 of the centers participating had annual transplant rates of ≥30 patients, and 50% of the centers had been in operation for 9 years or more. Lung transplant recipients are highly susceptible to fungal infections.1–9 They have rates of Aspergillus infection that exceed all other solid-organ transplant groups and are uniquely susceptible to Aspergillus tracheobronchitis.5,9,12 Aspergillus infections may be difficult to diagnose and once established are often resistant to treatment and carry a mortality rate of >50%.6–10,12,13 Thus, it is not surprising that most centers use anti-fungal prophylaxis or pre-emptive therapy, even in the absence of controlled studies. The rationale for this current survey was to obtain an overview of current anti-fungal practices, in an effort to promote further investigation in this area. Whenever studies are devised, it is important to have a grasp of the current standard of care. This is particularly true with multicenter studies for which a consensus needs to be reached among researchers at different centers. It also is useful to note where current practice agrees with or diverges from available observational data.

This study focused on 3 major areas: pre-emptive therapy before transplantation, prophylaxis, and pre-emptive therapy after transplantation. We found that a sizable majority (81%) of centers performed fungal surveillance before transplantation, although some restricted these investigations to patients who were more likely to be colonized. The interventions used for positive fungal culture results diverged sharply depending on the fungus isolated. A sizable majority of the centers treated patients who had Aspergillus spp isolation, but most centers ignored isolation of Candida spp. The best available observational data suggest that patients colonized with Aspergillus before transplantation are not at greater risk for Aspergillus infection after transplantation.14–16 This disparity between clinical observation and clinical practice suggests that a controlled, prospective trial would be helpful to define best practice. Our survey suggests that oral azole therapy would be the most acceptable medication to use in such a study.

After transplantation, 75% of programs used prophylaxis. This was started promptly after transplantation;
85% of centers began anti-fungal prophylaxis by 3 days after transplant surgery. We found less consensus on which agent to use. A sizable proportion of centers used itraconazole and inhaled amphotericin, whereas only a minority used parenteral amphotericin. This variability in practice is not surprising because all of these approaches have received some support from observational studies. The duration of anti-fungal prophylaxis was quite variable, with a median duration of 3 months. However, the majority of centers (70%) used anti-fungal prophylaxis for 6 months.

Our survey results show that most centers institute some form of anti-fungal prophylaxis after transplantation. Therefore, it is unlikely that a large placebo-controlled study of fungal prophylaxis could be accomplished after lung transplantation. It may be feasible, however, to design a study to compare anti-fungal agents of different classes for effectiveness and tolerance. The duration of such a study should be reasonably consistent with current practice and a length of 3 months may be acceptable to many centers.

Finally, our survey suggests that studies of pre-emptive therapy may be difficult. There is such a high level of concern for Aspergillus colonization that placebo-controls are not likely to be acceptable. Our survey also suggests that there is already a strong preference for oral azole therapy rather than amphotericin-based therapy. Thus, acceptable comparators would have to be available orally. Also, the variable timing of colonization and the preceding history of anti-fungal treatment may introduce many confounding variables into the study. Finally, it will probably be difficult to find acceptable objective end-points for such a study because the rate of invasive fungal infection is small in colonized patients who receive pre-emptive therapy. Our analysis of the association between demographic factors and the centers' choice of prophylactic or pre-emptive regimens did not produce very interesting results. Neither size nor experience seemed to play a very important role in decisions about anti-fungal management. Likewise, we could not find differences in approach related to the availability of a transplant infectious disease specialist. With the latter question, however, we did not make any effort to specify the degree of the transplant infectious disease specialist's involvement in developing protocols.

Future progress in understanding and managing fungal infections after lung transplantation likely will depend on the ability to carry out larger, multicenter, prospective studies. Despite the inherent difficulties of such studies, their progress may be facilitated by the availability of new diagnostic techniques for Aspergillus, such as polymerase chain reaction and double-sandwich enzyme-linked immunosorbent assay, as well the introduction of new anti-fungal medications that require evaluation in immuno-compromised populations.

The authors thank Ben H. Lewis, BBA, for developing the web-based questionnaire.

REFERENCES

12. Kramer MR, Denning DW, Marshall SE, et al. Ulcerative...

APPENDIX I
The following lung transplant programs contributed to this survey:

Barnes Jewish Hospital
Baylor University Medical Center
Brigham and Womens Hospital
Children's Hospital Los Angeles
Children's Hospital of Wisconsin
Cleveland Clinic
Duke Medical Center
Fairview University Medical Center
Henry Ford Hospital
Hospital of the University of Pennsylvania
Inova Fairfax Hospital
Jewish Hospital
Johns Hopkins Hospital
Loyola University Medical Center
McGuire Veterans Administration Medical Center
Medical College of Virginia Hospital
Mount Sinai Hospital
Ochsner Foundation Hospital
Ohio State University
Oklahoma Transplant Institute
Oregon Health Sciences University
Shands Hospital at the University of Florida
St. Louis Children's Hospital at Washington University Medical Center
The Methodist Hospital Baylor College of Medicine
University of California Davis Medical Center
University Hospitals of Cleveland
University of Alabama-Birmingham
University of California San Francisco Medical Center
University of Colorado Hospital
University of Maryland
University of Miami/Jackson Health Systems
University of North Carolina
University of Texas Medical Branch
University of Texas Southwestern
University of Virginia
University of Southern California Cardiothoracic Transplant Program
Vanderbilt University Medical Center