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FUNGAL INFECTIONS IN LIVER TRANSPLANT RECIPIENTS[1]

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Sixty-two adults who underwent orthotopic liver transplantations between February 1981 and June 1983 were followed for a mean of 170 days after the operation. Twenty-six patients developed 30 episodes of significant fungal infection. *Candida* species and *Torulopsis glabrata* were responsible for 22 episodes and *Aspergillus* species for 6. Most fungal infections occurred in the first month after transplantation. In the first 8 weeks after transplantation, death occurred in 69% (18/26) of patients with fungal infection but in only 8% (3/36) of patients without fungal infection ($P<0.0005$). The cause of death, however, was usually multifactorial, and not solely due to the fungal infection. Fungal infections were associated with the following clinical factors: administration of preoperative steroids ($P<0.05$) and antibiotics ($P<0.05$), longer transplant operative time ($P<0.02$), longer posttransplant operative time ($P<0.01$), duration of antibiotic use after transplant surgery ($P<0.001$), and the number of steroid boluses administered to control rejection in the first 2 posttransplant months ($P<0.01$). Patients with primary biliary cirrhosis had fewer fungal infections than patients with other underlying liver diseases ($P<0.05$). A total of 41% (9/22) of *Candida* infections resolved, but all *Aspergillus* infections ended in death.

Fungal infections have been reported following abdominal surgery (*1, 2*), in hematologic and other malignancies associated with leukopenia, (*3–5*) and in other immunosuppressed individuals including transplant patients (*6, 7*). A high rate of *Candida* and other fungal infections has been documented by Schroter et al. (*8*) in liver transplant patients on azathioprine and prednisone immunosuppression. Recently, we reported that liver transplant patients on cyclosporine and prednisone had a higher incidence of serious fungal infections than kidney, heart, and heart and lung transplant patients on comparable immunosupression (*9, 10*)

Many authors have sought to specify factors that predispose to fungal infection (*1, 6, 7, 11*) but few have based their analyses on a group of patients with similar diagnoses or procedures. We studied fungal infections in a group of 62 adult liver transplant recipients treated with cyclosporine and steroids, in order to define factors that influenced the development of these infections, and to determine the morbidity and mortality associated with them.

MATERIALS AND METHODS

Sixty-nine adults received orthotopic liver transplants at Presbyterian-University Hospital between February 1981 and June 1983. Information regarding their course was gathered by review of in-patient and out-patient charts. Six patients who died within 24 hr of the operation and one patient whose chart was unavailable were excluded, leaving 62 analyzable patients. Follow-up ranged from 4 to 594 days (mean: 170 days), and survivors were followed for at least 2 month. Fifteen retransplantation operations were performed, twelve during the first two months of follow-up.

All patients were treated with cyclosporine and corticosteroids. Prophylactic antibiotics included a cephalosporin and a penicillin or an aminoglycoside administered before the operation and for various periods after surgery. In addition, the patients received nystatin 400,000 IU orally four times a day beginning at transplantation and continuing at least throughout their initial hospitalization. The technical details of the operation and postoperative care have been described previously (*12*).

An attempt was made to include only significant fungal infections. These required (1) isolation or histologic evidence of a fungus from an ordinarily sterile site or a site not usually colonized by fungi, and (2) histologic evidence of tissue invasion and/or other clinical or laboratory evidence of significant in-

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fection such as positive cultures from multiple sites, the presence of an abscess or empyema, and clinical abnormalities such as fever, leukocytosis, or pyuria. Patients who satisfied only criterion 1—such as those with colonization and trivial infections represented by isolations of fungi, usually *Candida*, from throat, skin, urine, or sputum, nasotracheal aspirates, and surgical drainage tubes without associated clinical abnormalities—were excluded. Dissemination was defined as the presence of fungal infection in two or more sites separated by anatomical tissue planes (e.g., thorax and abdomen, thyroid and brain).

Candida infections included all those identified as *C. albicans*, *C. tropicalis*, and *C. stellatoidea*. *Torulopsis glabrata* infections were also included.

An infection was defined as associated with death when it was a major diagnosis at autopsy—or, if no autopsy was performed, when the infection was an important concern in the care of the patient at the time of death. An episode of infection was defined as a single occurrence during which the patient was infected with the same genus of fungus regardless of the number of cultures or sites from which it was isolated. Concurrent infections with different genera were counted as separate episodes.

To identify preoperative and postoperative factors associated with the development of fungal infections, the group was first divided into patients who developed a fungal infection after transplantation and those who did not. Then the frequency of risk and associative factors in these two groups was determined. Preoperative factors studied were the pathologic diagnosis of the patient's liver disease, the use of systemic steroids within three months prior to the operation and the use of systemic antibiotics within a two-week period before transplantation. Immediate pretransplantation steroids and prophylactic antibiotic therapy were not counted, because all patients received such therapy. Preoperative liver function and nutritional status were assessed by reviewing the patients' preoperative prothrombin times, partial thromboplastin times, and serum albumin levels. The duration of operative time was taken as the time from first skin incision to skin closure, as indicated on the anesthesia record.

Postoperative factors studied were the total operative time of all posttransplant reoperation(s)—either for correction of technical deficiencies and/or subsequent retransplantations, the duration of antibiotic therapy, the number of bacterial infections, and the number of presumed rejection episodes. The duration of antibiotic therapy was defined as the number of days a patient received any systemic antibiotic divided by that patient's total days of follow-up in the first month. Courses of antifungal therapy were not included. The presence of bacterial infection was determined by positive culture from a normally sterile site if the isolate was clinically determined to be significant. Two indices of rejection were used. First, the number of i.v. boluses of 100 mg or more of hydrocortisone (or equivalent) given in addition to normal maintenance steroid therapy were summed and divided by the total number of follow-up days in the first and second months. The routine bolus that patients received immediately postoperatively was not counted. Second, the number of recycles of steroids, defined as the administration of high doses of oral steroids with daily decrements for about 5 days until maintenance dosages were achieved, were similarly summed and divided by the total follow-up days in the first two follow-up months. Thus numbers were obtained for each patient that represented mean bolus frequency and mean recycling frequency.

Statistical comparisons between the two groups were made using chi-squared analysis (to compare proportions) and the unpaired t test (to compare means). Differences were considered significant if the P value was less than 0.05.

RESULTS

The 62 patients consisted of 28 male and 34 female patients (Table 1). Twenty-six patients (42% of the total group) had 30 episodes of fungal infection including four patients with two fungal infections. Fourteen male patients had 17 fungal infections (three with two episodes each) and 12 female patients had 13 infections. There was no signficant difference in the proportion of male or female patients developing fungal infection or in their mean number of infections. Twenty-nine (47%) of the patients died during the follow-up period, and 20 (69%) of the patients who died had fungal infections.

Table 2 shows the type of fungal infections and their courses. *Candida* caused 73% and *Aspergillus* species 20% of all fungal infections. *Cryptococcus* and *Mucor* each caused one significant infection. Single fungal infection was associated with 18 deaths; one patient had two fungal infections at death (*Candida* and *Mucor*). All six patients with *Aspergillus* infection died. *Candida* infection was present at death in 13 cases. Nine episodes of

TABLE 1. Fungal infections in liver transplant recipients

	All patients	Male patients	Female patients
Number	62	28	34
No. with fungal infections (%)	26 (42%)	14 (50%)	12 (35%)
Episodes of fungal infection per patient	30/62 (0.48)	17/28 (0.61)	13/34 (0.38)
Deaths, all causes	29/62 (47%)	17/28 (57%)	13/34 (38%)
Deaths associated with fungus infections	20/62 (32%)	10/28 (36%)	9/34 (26%)

TABLE 2. Type and course of fungal infections

	Candida	*Aspergillus*	*Cryptococcus*	*Mucor*	Total
No. episodes	22 (73%)[a]	6 (20%)	1 (3%)	1 (3%)	30 (100%)
No. disseminated	10	4	1	0	16
Episodes associated with death	13 (59%)[b]	6 (100%)[c]	0	1	20
Episodes resolved	9 (41%)[b]	0 (0%)[c]	1	0	10

[a] Percentages of all fungal episodes.
[b] Percentage of all *Candida* infections.
[c] Percentage of all *Aspergillus* episodes.

Candida infection and one episode of cryptococcal infection resolved.

Figure 1 shows the time of onset and type of fungal infections in the patients studied. Of all fungal infections, 80% (24/30) occurred in the first month after transplant, and 90% occurred in the first two months after transplant. Among the candidal infections 19 of 22 and among the *Aspergillus* infections 4 of 6 were diagnosed in the first four weeks after transplantation. Only three fungal infections were seen after the first two months of follow-up.

Figure 2 shows that only 3 (8%) of 36 patients without fungal infection, but 18 (69%) of 26 patients with fungal infection, died in the first 8 weeks after transplantation ($P<0.001$). Only four patients with fungal infection survived the overall follow-up period. Of the 36 patients without fungal infection, 3 died in the first 8 weeks and a total of 7 died overall. This difference in survival between the two groups for the total follow-up period was also significant ($P<0.001$).

Details of the clinical episodes of fungal infection are given in Tables 3, 4, and 5. Table 3 lists *Candida* infections that resolved, Table 4 *Candida* infections that did not resolve, and Table 5 other fungal infections. Some of the infections listed in Table 3 might be considered localized or minor. A number of these patients had definite tissue evidence of invasive infection, and three patients subsequently developed *Aspergillus* infections confirmed at autopsy. This occurred despite amphotericin therapy (patients 38, 43, and 46).

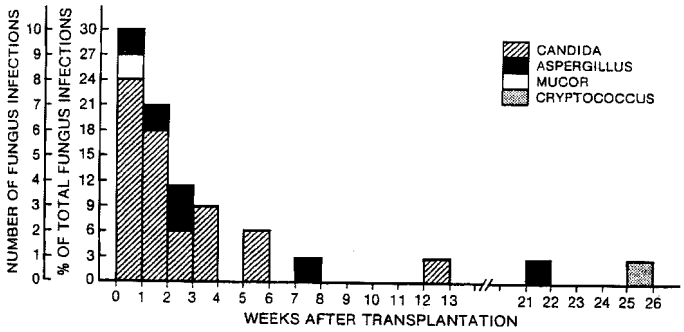

FIGURE 1. Number of episodes of fungal infections in liver transplant recipients by day of first isolate.

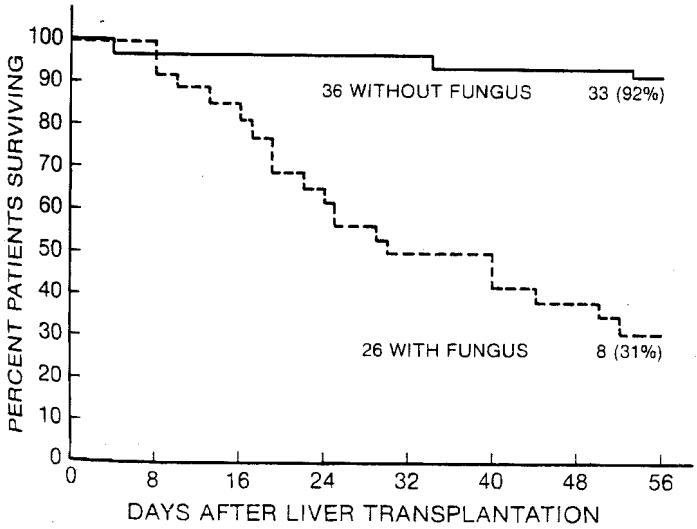

FIGURE 2. Survival of liver transplant recipients with and without fungal infections.

Risk factors and associative factors. The patients' underlying hepatic pathologies are shown in Table 6. There were 16 female patients with primary biliary cirrhosis (PBC).[3] Eighteen patients had chronic active hepatitis or postnecrotic cirrhosis, or both. Eight patients had primary carcinoma of the liver or cholangiocarcinoma. Six had sclerosing cholangitis. Among the 14 "others" were 3 patients with alpha-1 antitrypsin deficiency. Two patients each had Caroli's disease, atypical biliary cirrhosis, and acute hepatic failure due to toxins. One patient each had Budd-Chiari syndrome, multiple adenomas of the liver, hemachromatosis, tyrosinemia and biliary hypoplasia. Patients with PBC had a better overall survival than other patients ($P<0.05$) and fewer patients with PBC developed fungal infections ($P<0.05$).

Preoperative synthetic liver function was compared in the groups of patients with or without fungal disease. There was no significant difference in their liver function as estimated by their mean preoperative prothrombin times, partial thromboplastin times, or serum albumin levels (data not shown).

Data on the use of systemic steroids three months before liver transplantation were available for 58 patients. Fourteen patients received preoperative steroids and 9 (64%) of these later developed fungal infections. Only 15 (34%) of 44 who did not receive systemic steroids developed fungal infections. This difference was significant ($P<0.05$).

Information on antibiotic use in the two weeks prior to liver transplantation was available for 59 patients, 25 of whom developed fungal infections. Twenty-three patients received antibiotics in this interval and 14 (61%) of them later developed fungal disease; 11 (31%) of 36 patients not receiving preoperative antibiotics developed fungal infection after transplant ($P<0.05$).

The operative times of the patient groups were compared. Those who developed a fungal infection after transplantation had operative times ranging from 7.6 h to 18.8 h (mean = 13.1 h). The operative times for patients who did not subsequently develop a fungal infection ranged from 6.8 h to 18.3 h (mean = 11.1 h). This difference was significant ($P<0.02$). The total time of all operations in the first month after the initial liver transplant ranged from 0 to 15 h (mean = 4.3 h) for those who subsequently developed a fungal infection and from 0 to 9.1 h (mean = 1.4 hr) for those who did not. This difference was also significant ($P<0.01$).

The incidence of fungal infection was not affected by the type of biliary drainage procedure. Most (81%) of patients had primary biliary anastomosis, including 20/26 (77%) of patients with fungal infection and 30/36 (83%) without fungal infection.

Figure 3 presents a comparison of the proportion of patients who received antibiotics during four weeks after transplantation in the two groups. On the average, the group with fungal infections were on systemic antibiotic 78% of the time, compared with 53% for the group without fungal infection ($P<0.001$). Thus patients who developed fungal infections had more sustained antibiotic therapy than the patients who did not develop fungal infections.

Of the 26 patients with fungal infections, 21 (81%) had one or more documented bacterial infections. Of the 36 patients without fungal infection, 15 (42%) had bacterial infections

[3] Abbreviation used: PBC, primary biliary cirrhosis.

TABLE 3. Resolved episodes of candidal infections

Patient no.	Sites infected or pathology	Day of first culture posttransplant	Note
12	Blood, abdominal abscess	12	Treated for 1 month; patient survived
15	Urine, sputum, liver (biopsy)	25	Treated for 1 month; patient survived
28	Bile, abdominal hematoma, peritoneal fluid	9	Bile leak repaired, drained; patient survived
32	Urine, sputum, peritoneal fluid, pleural fluid	11	Infiltrate and effusion, treated, patient died 72 days posttransplant, no autopsy
38	Wound, abdominal hematoma	26	Treated for 18 days[a]
43	Bile, peritoneal fluid, sputum, chest drain	7	Treated for 12 days[a]
44	Wound abscess, sputum, drain	13	Treated for 8 days, patient survived
46	Sputum, thoracentesis	9	Treated for 7 days[a]
54	Urinary tract	9	Treated for 1 month

[a] See Table 5.

TABLE 4. Candidal infections associated with death

Patient no.	Sites infected or pathology	Day of first culture posttransplant	Day of death	Note
1	Wound, peritoneum, lung chest tube, blood, urine	19	23	Autopsy confirmed
2	Abdominal abscess, wound chest tube, splenic capsule	6	14	No autopsy
4	Blood, peritoneal fluid	5	17	Autopsy confirmed[a]
19	Blood, peritoneum, liver, kidneys, heart, lungs	87	91	Autopsy confirmed
24	Blood, peritoneum, liver, spleen	24	30	Autopsy confirmed
31	Peritoneum, rectus sheath abscess	19	20	No autopsy
33	Pleural fluid, peritoneal fluid, blood, urine, kidneys, wound, heart, abdominal abscesses, lung	4	50	Autopsy confirmed
34	Urinary tract, peritoneum	6	9	Limited autopsy, not confirmed
35	Urine, sputum, t-tube blood	20	41	Treated for 8 days till death, autopsy not confirmed
45	Abdominal hematoma, wound, urine, sputum, chest tube drainage, paracentesis fluid	2	26	Treated for 11 days till death, no autopsy
50	Esophagus, stomach, duodenum, kidneys, knee, lymph node, blood, lung, spleen, heart, liver, adrenal, thyroid	9	9	Autopsy confirmed
58	Sputum, wounds, urine	2	19	Treated for 2 days till death; no autopsy
62	Sputum, urine, wounds	24	44	Treated for 3 days till death; no autopsy

[a] See Table 5.

($P<0.01$). Despite the strong statistical association between bacterial infection and fungal infection, there was no clear temporal sequence between bacterial and fungal infections.

Patients with PBC were found to have a lower risk for the development of fungal infections, so the prevalence of the risk factors discovered above was evaluated in these patients. Compared with transplant recipients with other liver diseases, fewer recipients with PBC had antibiotics before transplantation

TABLE 5. Other serious fungal infections

Patient no.	Organism	Sites infected or involved	Day of first culture posttransplant	Day of death	Note
4	*Mucor*	Wound	7	17	Autopsy confirmed
6	*Cryptococcus*	Meninges, blood	175	439	Treated, recovered
7	*Aspergillus*	Lung, heart, kidneys, esophagus, diaphragm, brain, rectum, spleen, stomach, colon, thyroid, pleura, lymph nodes	7	9	Autopsy confirmed
20	*Aspergillus*	Lung	151	151	Autopsy confirmed
38	*Aspergillus*	Lung, heart, thyroid	52	52	Autopsy confirmed
43	*Aspergillus*	Lung	16	25	Autopsy confirmed
46	*Aspergillus*	Lung, bladder, stomach, thyroid, pleural fluid, heart	25	25	Autopsy confirmed
48	*Aspergillus*	Lung, kidneys, pleural fluids, brain, thyroid	13	17	Autopsy confirmed

TABLE 6. Relationship of fungal infections to pretransplant liver pathology

Diagnosis	N	Fungal episodes per patient	Percentage of patients with fungal infections	Mortality
Primary biliary cirrhosis	16	0.19 (3/16)	19% (3/16)[a]	19% (3/16)
Chronic active hepatitis and/or postnecrotic cirrhosis	18	0.56 (10/18)	50% (9/18)	56% (10/18)
Carcinoma and hepatoma	8	0.25 (2/8)	25% (2/8)	50% (4/8)
Primary sclerosing cholangitis	6	0.5 (3/6)	50% (3/6)	50% (3/6)
Others	14	0.86 (12/14)	64% (9/14)	64% (9/14)
Total	62	0.48 (30/62)	42% (26/62)	47% (29/62)

[a] Primary biliary cirrhosis patients compared with all other patients ($p<0.05$).

($P<0.02$). Also, their transplant operations were of shorter duration ($P<0.02$), their total operative time during the first month after transplantation was shorter ($P<0.001$), and they were on antibiotics for fewer days after transplantation ($P<0.05$). These patients had less-complex operations, fewer postoperative complications, less use of antibiotics before and after transplantation, and fewer bacterial infections. No difference was found between patients with PBC and other patients in preoperative steroid usage or synthetic liver function.

Fungal infections and rejection. Rejection of the liver was usually determined clinically (rather than histologically), so we assessed the impact of rejection on fungal infections in terms of antirejection treatment—namely, the number of steroid boluses and number of recycles of steroid therapy in the first and second posttransplant months. The mean number of boluses in the first month was 0.21 per day for patients with fungal infection, and 0.15 per day for those without fungal infection. Over a follow-up period of two months, the means were 0.20 per day and 0.13 per day. The difference was not significant for the first month of follow-up ($0.05 < P < 0.1$) but was at two months of follow-up ($P<0.01$). A recycling of steroids usually takes five days. Over the total 2 months of followup the patients with fungal infections received a mean of 0.96 recycles per patient and those without fungal infections received a mean of 0.89 recycles per patient. This difference was not significant. Thus i.v. steroid boluses may have been related to the development of fungal infections, but the relation of recycles of steroids to the development of fungal infections was less clear because almost all patients received recycling therapy.

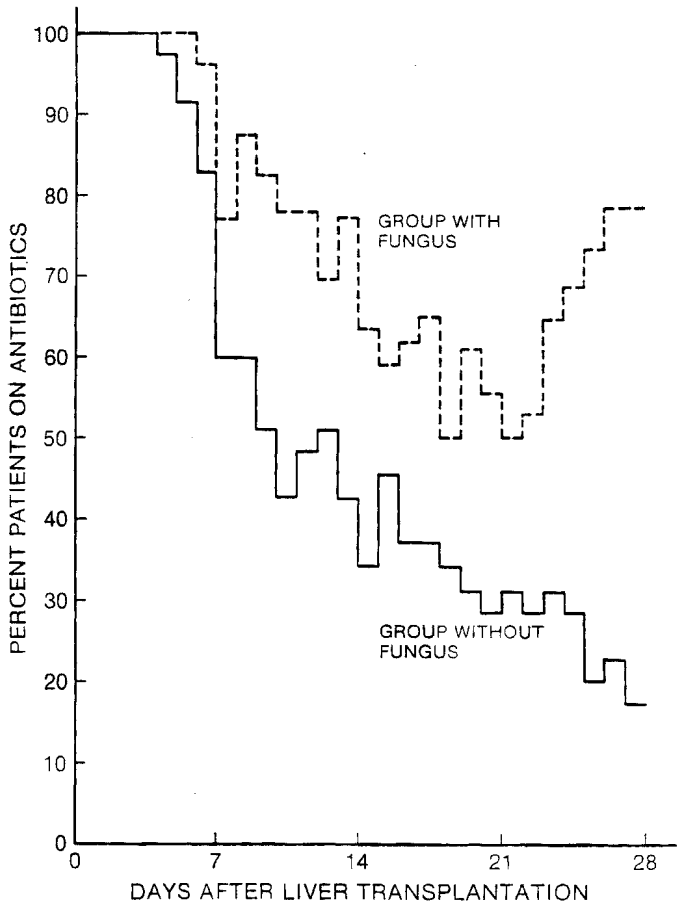

FIGURE 3. Antibiotic use in patients with fungal infections expressed as the percentage of surviving patients who were on antibacterial antibiotics.

A final measure suggests a relationship between fungus infection and rejection. During the first month after transplantation, 7 of 26 patients with fungal infection were retransplanted, while only 2 of 36 without such infections were retransplanted. This difference is significant ($P < 0.05$), and it may also be related to the difference in the total operative time after transplantation between the two patient groups. The number of retransplantations in the infected and uninfected groups for the total follow-up period (9 and 6, respectively) was not significantly different.

In summary, various measures of rejection suggest a relationship between fungus infection and rejection. Whether the development of fungal infection was associated with the immunological process of rejection or its treatment (steroids and retransplantation) could not be determined by our analysis.

DISCUSSION

The clinical significance of fungal infections may be difficult to determine (*5*). Schroter et al. (*8*) noted 29 (33%) invasive fungal infections in 87 liver transplant recipients treated with azathioprine, steroids and antilymphocyte globulin. This is not different from our findings (26/62 or 42%). Even so, these authors employed a definition of fungal infection somewhat different from ours. They noted 31 instances of "infestation" that included the isolation of *Candida* from urine, blood, and other normally sterile sites, and 26 more cases of colonization. Neither infestations nor colonizations were included in their list of "infections," even though some of these cases were treated with amphotericin. Our definition of infection would include some "infestations" by their definition. To help the reader interpret our categories, details of the candidal infections included here are given in Tables 3 and 4.

Twenty-nine of the 62 patients in this series died during the follow-up period. This is an improvement in survival over that seen in the past in patients treated with azathioprine (*13, 14*). Fungal infections were present at death in 19 of these 29 patients.

Most patients who died with fungal infections also had other conditions that contributed to their demise, such as graft rejection or necrosis, bacterial or viral infections, or hemorrhage. Of 19 autopsies performed, fungal infection was listed as a cause of death in ten. A high mortality has also been noted in other series of immunosuppressed patients with serious fungal infections (*3, 6*). All patients with *Aspergillus* infections died, but 41% (9 of 24) of candida infections resolved. Eight of these nine patients received amphotericin therapy, and one underwent surgical drainage of an infected abdominal hematoma. A patient with cryptococcal septicemia and mengingitis was cured, and the patient with *Mucor* wound infection died, but that infection was not a direct cause of death. It is clear from Figure 2 that fungal infections in liver transplant patients are associated with a very poor prognosis.

One cryptococcal infection, ten *Candida* and four *Aspergillus* infections fulfilled our definition of dissemination. All of these except the cryptococcal infection were associated with death. Whether early treatment of these infections would have prevented dissemination is unknown. It should be noted that three patients were treated with amphotericin and recovered from *Candida* infections, but later developed aspergillosis. In these patients, at least, amphotericin did not prevent a subsequent fatal fungal infection. This may be germane to studies of prophylactic amphotericin in these compromised hosts.

Most fungal infections occurred within one month of liver transplant surgery (Fig. 1). This is somewhat earlier than the fungal infections described in renal transplants (*7*) and general surgical patients (*3*). The difference may be due to the often poor preoperative condition of the liver transplant patients or related to one or more of the risk factors discussed below. It shows that careful vigilance with regard to fungal infection must be maintained in the early post-operative period.

The gastrointestinal tract is an important source of *Candida*, which colonizes 30 to 60% of normal subjects (*15*). Liver transplantation disrupts the biliary tract and bowel, so *Candida* may be released during the operative procedure. Other *Candida* infections may be related to catheters and instrumentation. We did not specifically count the number of catheters in each patient, but all patients had i.v. and intraarterial catheters at some time in their course. In contrast to *Candida*, *Aspergillus*, *Cryptococcus*, and *Mucor* are not endogenous organisms and are probably acquired from the physical environment.

The factors we found to be associated with fungal infections are as follows:

A. Factor associated with decreased risk of infection: primary biliary cirrhosis
B. Factors associated with increased risk of infection:
   1. Preoperative steroids
   2. Preoperative antibiotics
   3. Duration of transplant operation
   4. Duration of posttransplant operations
   5. Duration of posttransplant antibiotics
   6. Bacterial infections
   7. Treatments for rejection

Certain factors have been previously reported to promote fungal infection. These are debility, malnutrition, hyperalimentation, antibiotics, steroids, indwelling catheters, diabetes mellitus, and surgical procedures—especially those involving the gastrointestinal tract (*3, 6, 7, 11, 16*). Most studies of these factors have been in patient groups with mixed diagnoses or in patients who had undergone a variety of surgical procedures. Some are deductions from case reports (*16*) or animal studies (*17*). Leukopenia is one important risk factor for disseminated candidiasis that is seen primarily in patients with acute hematologic malignancies (*4*). It was not found in our patients.

Preoperative prothrombin times, partial thromboplastin times, and serum albumin levels were analyzed as an indicator of the patients' nutritional status and liver function. We found no difference in these parameters between those who did and did not develop a fungal infection.

The use of antibacterial agents has been hypothesized to allow over-growth of endogenous fungi and thus predispose to serious fungal infection (*16*). The patients who developed fungal infection were more likely to have received antibiotics in the 2 weeks before transplantation. We conclude that preoperative antibiotic therapy does predispose to subsequent fungal infection. Whether this is due to increased colonization or some other factor is not clear (*16*).

In experimental models, steriods have increased the severity of fungal infection (*17*). We found that steroid treatment in a 3-month period prior to transplantation was associated with the subsequent development of fungal infections.

Longer operative times were also a risk factor. It is not possible to segregate the precise reasons for this finding. Longer operative times may be associated with a patient's metabolic

or hemostatic problems or reflect technical problems at surgery. Clearly, longer operative times also result in longer exposure of the operative field to the environment.

The intensity of antibiotic use after the operation was also associated with the occurrence of fungal infection. As would be expected from this finding, patients with fungal infections were more likely to have bacterial infections. In our patients we found no clear temporal sequence to suggest a cause-effect relationship. Interestingly, some authors have found a correlation between fungal infection and concurrent bacterial infection, but no correlation with use of antibiotics (*6*, *7*).

An important concern is whether infections are associated with rejection of the liver transplant. The precise diagnosis of rejection in liver transplant recipients is often difficult, and tissue evidence is not always available. For this reason we used the institution of treatment regimens as our measure of rejection. Of three treatment regimens studied, the number of boluses of steroids and the frequency of retransplantation in the first month were significantly associated with fungal infections. We have also investigated the association of bacterial and viral infections with rejection using these treatment criteria. Bacterial infections, but not cytomegalovirus infections, were associated with rejection as measured by steroid boluses (Ho M, unpublished data). In this analysis it is not possible to conclude whether fungal and bacterial infections are a result or a cause of rejection, or whether they are related to antirejection treatments.

Fungal infections have been noted to occur more frequently in male patients (*6*, *7*). In our study comparison of the number of male and female patients with fungal infections showed no differences. An important finding was that there were fewer fungal infections and fewer deaths in patients with a preoperative diagnosis of primary biliary cirrhosis ($P < 0.05$), all of whom were female. Recipients with this diagnosis were less likely to have received antibiotics preoperatively, their transplant operations were of shorter duration, their total operative time in the one month posttransplant was shorter, and they had fewer mean days of antibiotic therapy ($P < 0.05$). Hence, we found no clear influence of sex on fungal disease despite the female preponderance in primary biliary cirrhosis.

In summary, we find fungal infection to be a common, and at times devastating, disease in the liver transplant population. Our findings lend support to those who think that antibiotics, steroids, and surgical trauma increase the risk of fungal infections. Patients with fungal infection did receive more i.v. steroids for rejection, and were more likely to undergo retransplantation for graft loss. Patients with primary biliary cirrhosis did have a low incidence of fungal infection and a better chance of survival. The rate of fungal infection in our series was not different from that reported for liver transplant patients treated with azathioprine, prednisone, and antithymocyte globulin, despite the overall improvement in survival of liver transplant patients with cyclosporine therapy. There may be unique factors in liver transplantation that will make the eradication of fungal infection difficult, but attention to the risk factors mentioned here, especially the judicious use of antibiotics and steroids, may help to decrease the number of fungal infections seen in these patients. The possible importance of monitoring immunosuppression must be evaluated in a separate context.

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