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Infections after Liver Transplantation

AN ANALYSIS OF 101 CONSECUTIVE CASES

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Introduction

Liver transplantation is now practiced at many centers around the world (3). Many studies have been published on the results and complications of liver transplantation in the azathioprine era (23, 24). Since the introduction of cyclosporine (CyA), significant progress has been made in overall survival after transplantation (22).

We previously described high rates of infection in small groups of patients who received transplants between 1981 and 1983 in Pittsburgh (7, 11). However, no large, comprehensive study of infections in liver transplant recipients has been published after cyclosporine has been routinely monitored, after further improvement in surgical techniques (21) and the routine use of venous bypass (20). This is a study of the frequency, timing, and risk factors for infections in 101 consecutive adult liver transplant recipients at the Presbyterian-University Hospital (PUH), University of Pittsburgh, from July 1984 to September 1985.

Data were collected on all infections; subdivided according to severity; classified by major pathogen as bacterial, fungal, viral or protozoal infections. The timing and associated mortality for the most frequent severe infections were ascertained.

An attempt was made to determine risk factors for severe infection. Pretransplant factors analyzed were: age, sex, diagnosis, clinical status, corticosteroids and antibiotic use, and 25 laboratory values obtained during initial evaluation before transplantation.

Surgical factors analyzed were: total number of abdominal surgical procedures and the total number of hours spent in surgery, excluding operations for the drainage of abdominal abscesses.

Post-transplant factors analyzed were: the use of OKT3 antibody therapy, steroid boluses, and "recycles" and azathioprine and CyA levels for the first 3 post-transplant months. The monthly mean of the weekly median CyA level was employed for analysis.

Finally, the incidence of severe infection was related to the number of transfusions of packed red cells, platelets, fresh frozen plasma, and cryoprecipitate.

Methods

General population

The patient population included 101 consecutive patients who underwent liver transplantation between July 1984 and September 1985 and who survived for more than 72 hours. All patients were followed prospectively for infection. In addition, patient records were reviewed at the end of the study and follow-up information was obtained from referring physicians.

Surveillance cultures for cytomegalovirus and herpes simplex viruses (buffy coat, throat wash, urine) were performed every 2 to 4 weeks for the first 2 to 3 months after transplant on most patients. Other cultures were ordered as dictated by the clinical situation.

Antibiotic prophylaxis

Patients were treated with cefotaxime and ampicillin 4 g/day each for the 5 days after surgery. Oral mycostatin 400,000 units q.i.d. was given for *Candida* prophylaxis until discharge.

Surgery and immunosuppression

All patients underwent orthotopic liver transplantation as described by Starzl (21) either with primary anastomosis of the bile duct or choledochojejunostomy. Intraoperatively, a veno-venous bypass was employed to shunt blood from the portal system and inferior vena cava to the subclavian vein (20).

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Standard immunosuppression included cyclosporine (CyA) and corticosteroids. CyA was initially administered at a dosage of 2 mg/kg intravenously on the day of surgery and 6 mg/kg/day thereafter. As soon as the patient was able to take oral medication CyA was administered orally and adjusted to obtain blood levels of 800 to 1000 ng/ml by radioimmunoassay (RIA).

One gram of methylprednisolone was administered intravenously on the day of surgery. This was reduced to 200 mg on the day after surgery and then rapidly tapered so that by day 6 the patient was receiving 20 mg of methylprednisolone. Oral therapy with an equivalent dose of prednisone was employed when the patient was able to take oral medicine.

Rejection episodes were treated with either increased doses of steroids or intravenous OKT3 monoclonal antibody (Ortho Pharmaceutical Corporation). Steroid antirejection therapy consisted either of 1 g boluses of Solu-Medrol or a "recycling" of oral prednisone in which the daily dose of prednisone was raised to 200 mg/day and tapered to maintenance levels over 5 days. Azathioprine was also administered to some patients, generally when cyclosporine doses had to be decreased because of nephrotoxicity.

Definitions of infections

We attempted to identify all infections which occurred after transplantation and categorize them according to time after transplantation, site of infection, type of pathogen, severity, and outcome. Strict criteria were employed to define infections included in this study. They are as follows:

Bacteremia was defined by the isolation in at least 1 blood culture of *Listeria monocytogenes, Staphylococcus aureus, Candida* species or aerobic gram-negative rods. For other pathogens the isolation of the bacteria in 2 blood cultures or in 1 positive blood culture and in a culture from a known site of infection was required.

Soft-tissue infection required the isolation of a pathogen from a soft-tissue site showing clinical signs of infection (such as erythema or purulent drainage) which required surgical intervention (such as incision and drainage, or debridement).

Peritonitis was diagnosed if the peritoneal neutrophil count was ≥ 300 polymorphonuclear cells and if a pathogen was isolated. In cases where no cell counts were obtained, a Gram stain of peritoneal fluid showing ≥ 1 polymorphonuclear cell per oil field was sufficient. In each case an abdominal abscess was excluded by scanning techniques or at laparotomy.

A *bacterial abscess* was defined as a collection of pus drained surgically or via percutaneous catheter. In practice, all abscesses in this series also yielded 1 or more bacterial pathogens on culture.

The diagnosis of *cholangitis* required the presence of fever, right upper quadrant pain, and elevation of liver function tests together with either evidence of cholangitis on liver biopsy or isolation of the same organism from both the T-tube drain and blood.

Pneumonia required the appearance of new infiltrates on chest radiograph, the onset of new respiratory symptoms (cough, dyspnea) or hypoxemia, ($Po_2 < 75$) and the isolation of bacteria in heavy growth from purulent sputum. The adequacy of sputum was determined microscopically by 1 of the authors. *Pneumocystis* pneumonia was diagnosed by 1 positive methenamine silver stain of open-lung biopsy or cytospin smear of bronchoalveolar lavage fluid.

When no Foley catheter was present, *urinary tract infection* was diagnosed by the isolation of $\geq 10^4$ bacteria (on 1 occasion) or $\geq 10^4$ yeast (on 2 occasions) and typical symptoms of urinary infection (dysuria, frequency) and/or pyuria (≥ 10 white blood cells per high power field). When a Foley catheter was present, either typical symptoms of pyelonephritis (flank pain, fever $\geq 38°C$) or a positive blood culture with the same organism isolated from the urine were required.

A diagnosis of viral syndrome due to *Cytomegalovirus* (CMV) required a temperature elevation $\geq 38°$ continuously or intermittently for at least 1 week without another known cause and one or more positive CMV cultures. In addition 1 of the following was required: atypical lymphocytes $\geq 3\%$, white cell count $< 4{,}000$ per mm^3, or platelets less than 100,000 per mm^3.

Diagnosis of tissue involvement with CMV, such as *CMV pneumonia, enteritis,* or *hepatitis* required tissue evidence of CMV infection either by direct culture from tissue or by histologic evidence (inclusion bodies).

Invasive candidiasis was diagnosed by either 1) a positive blood culture, 2) isolation of *Candida* from the abdomen at surgical exploration in association with peritonitis or an abdominal abscess, or 3) tissue invasion demonstrated by biopsy.

Invasive aspergillosis required evidence of tissue invasion on biopsy or at autopsy.

Herpes simplex virus (HSV) infection required typical oral or genital ulcers for diagnosis. A positive viral culture for herpes simplex virus was also required if a culture was submitted. Tissue invasion by biopsy was also acceptable evidence. Disseminated infection with HSV was diagnosed if 2 or more non-contiguous sites were infected.

An infection was considered to be associated with death if it was found at postmortem examination or if the patient was still under treatment for the infection when death occurred.

In order to concentrate our analysis on clinically significant events we categorized infections into *non-severe* and *severe infections.* Severe infections were those which would generally require hospitalization for treatment or diagnosis.

Non-severe infections were bacterial sinusitis, cystitis, localized herpes zoster infection, localized oral, genital and ophthalmic herpes. *Severe infections* included bacteremias, fungemias, deep tissue abscesses, peritonitis, pneumonia, wound infection, *Clostridium difficile* colitis, cholangitis, invasive candidiasis and aspergillosis, all symptomatic CMV infections and deep herpes simplex tissue infections such as disseminated herpes simplex infections, esophagitis, or hepatitis.

Statistics

Proportions were analyzed with chi-square test or if the numbers were small, Fisher's exact test; means were compared with Student's t-test.

Results

Description of the population

The study population consisted of 101 consecutive adult patients who underwent liver transplantation at PUH (Presbyterian University Hospital) between July 1984 and September 1985. The mean follow-up was 394 ± 219 (S.D.) days and 58 patients were followed for more than a year. The mean age was 39 years and the median age was 41 years.

Table 1 shows the underlying diagnosis and sex

of the recipients. Of the 101 patients, 39 were men and 62 were women. The diagnoses are divided in 3 main categories: hepatocellular diseases, cholestatic diseases, and a group of other diseases that could not be categorized. The most frequent diagnoses were: primary biliary cirrhosis (31 patients), chronic active hepatitis (17 patients) and sclerosing cholangitis (16 patients), and these accounted for 60% of the patients who received transplants.

Incidence of infections after liver transplantation and mortality

Table 2 shows the frequencies of total infections and severe infections in the population. As can be seen, 83% of all patients had an infection after transplant and 67% had severe infections. Almost all bacterial, fungal, and protozoal infections were severe, but less than one-half of viral infections (0.26/0.64 = 40%) were severe. Most non-severe viral infections were oral or genital herpes simplex infections.

TABLE 1. Underlying diagnosis of 101 liver transplant recipients

Diagnostic Category	Male	Female	Total
Hepatocellular (35 patients)			
Chronic active hepatitis	4	9	13
Cirrhosis, unknown etiology	3	3	6
Alpha-1 antitrypsin deficiency	2	2	4
Chronic active hepatitis B	4	0	4
Hemochromatosis	1	1	2
Alcoholic cirrhosis	0	2	2
Hepatoma after CAHB*	1	1	2
Wilson disease	0	1	1
Toxic-Thorotrast related	1	0	1
Cholestatic (51 patients)			
Primary biliary cirrhosis	5	26	31
Sclerosing cholangitis	9	7	16
Secondary biliary cirrhosis	0	3	3
Cystic fibrosis	1	0	1
Others (15 patients)			
Other liver tumors	3	4	7
Caroli disease	2	1	3
Fulminant hepatitis	1	2	3
Trauma	1	0	1
Budd-Chiari syndrome	0	1	1
Total	39	62	101

*CAHB = chronic active hepatitis with hepatitis B infection.

TABLE 2. Frequency of different infections in the study population

Type of Infection	% Patients Infected		Episodes of Infection per Patient*	
	All	Severe	All	Severe
Bacterial	59	54	0.89	0.79
Viral	53	24	0.64	0.26
Fungal	18	16	0.21	0.18
Protozoal	12	12	0.12	0.12
Total	83	67	1.86	1.35

*Abbreviated E/P in Tables 4, 5, 6, 8, and 9.

TABLE 3. Severe infections and those associated with 23 deaths in 101 patients

Infection	Number of Episodes	Associated with Deaths
Intra-abdominal abscess	16	5
Bacterial pneumonia	15	6
Soft tissue infection	10	2
Cholangitis	9	3
Peritonitis	7	3
Bacteremia, unknown source*	7	5
Pyelonephritis	7	0
Pseudomembranous colitis	6	0
Line sepsis	2	0
Endocarditis	1	0
Cytomegalovirus disease	22	5
Herpes simplex disease	3	3
Disseminated varicella	1	1
Invasive candidiasis	14	10
Aspergillosis	4	4
Pneumocystis carinii pneumonia	11	3
Toxoplasmosis	1	0
Total	136 episodes	

*There were 33 episodes of bacteremias; 26 were of known origin and are included in discussion of infection episode at specific sites (see text).

The overall mortality in the population was 26% (26/101). Twenty-three of the 26 deaths (89%) were associated with infection. The last death in the series occurred 357 days after transplantation. Most patients who died had multiple infections as well as other posttransplant complications so that a unique cause of death could not always be determined.

Table 3 shows all severe infections associated with 23 deaths. The most frequent severe infections were CMV disease (22 cases), abdominal abscesses (16 cases), bacterial pneumonias (15 cases), invasive *Candida* (14 cases) and *Pneumocystis* pneumonia (11 cases). Invasive candidiasis was the infection most often associated with a fatal outcome. Other infections which were frequently associated with deaths were intra-abdominal abscesses, cytomegalovirus infection, bacterial pneumonias, and bacteremias without a source. In order to concentrate the analysis on the most important infections, the remainder of this report will confine itself to the analysis of time of occurrence, clinical presentation, and risk factors for severe infections.

Incidence and time of occurrence of severe infections

Figure 1 shows the number of episodes of infections per patient per year (incidence) and the time of occurrence of severe infections after liver transplantation in the 101 patients. The rates of infection are based on the number and the length of follow-up of surviving patients during each time interval.

The most critical period for severe infections was the first 2 months after liver transplantation. This was true for severe bacterial, viral, and fungal in-

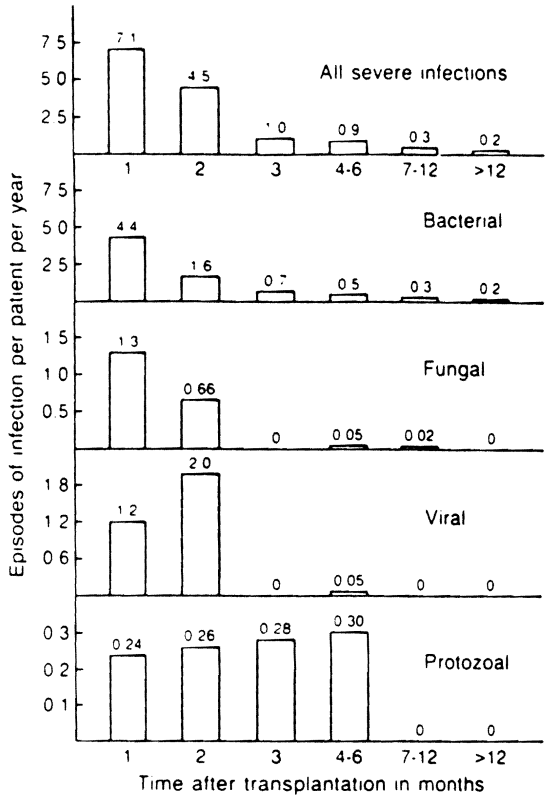

FIG. 1. Incidence in episodes of infections per patient per year and time of occurrence after transplantation when severe infections occurred.

fections. Severe viral and fungal infections which occurred more than 2 months after the initial transplant surgery all occurred within 65 days of a retransplant operation. Protozoal infections occurred at a constant rate during the first 6 months but were not diagnosed after that time.

Of 17 severe infections that occurred more than 6 months after transplantation, 16 were bacterial. The 17th case was fungal. This was a case of disseminated *Candida* infection in a patient 4 days after retransplantation with a third allograft.

Clinical manifestations

We describe in detail below the 136 most frequent severe infections, listed in Table 3. In some cases, data on the non-severe infections are given to round out the descriptions.

Abdominal abscesses: There were 9 abdominal and 7 liver abscesses. The 9 abdominal bacterial abscesses occurred in 7 patients and 4 of them (44%) were associated with bacteremia. The shortest onset was 9 days after liver transplantation and the longest was 331 days after the original transplant operation, but only 86 days after a third allograft was placed. Seven of the 9 abscesses (77%) were diagnosed within 30 days of a preceding abdominal operation.

Five abscesses were diagnosed by computerized scanning or ultrasound, and 1 was diagnosed at laparotomy after a plain abdominal film showed air under the diaphragm (secondary to colonic perforation). The other 3 had radiologically guided aspiration after clinical diagnosis. The location of the abscesses was quite variable. Splenic, pericolic and pelvic abscesses were also seen in addition to abscesses around the liver. All abscesses were treated with drainage and antibiotic therapy. Three (33%) were associated with death.

Seven liver abscesses were diagnosed in 6 patients. Five of the 7 abscesses occurred less than 30 days after liver transplantation or a subsequent abdominal operation. One abscess occurred 1 day after a third allograft was placed. The latest onset was 14 months after transplantation and this abscess was thought to be secondary to stenosis of the hepatic artery. All of the patients with liver abscesses had technical problems involving the implanted liver. These complications included thrombosis of the hepatic artery and inferior vena cava (2 patients), biliary leak (1 patient), biliary sludge (1 patient), and a tear in the donor liver (1 patient).

The organisms involved were *Enterococcus*, aerobic gram-negative enteric organisms, and anaerobes. Four of 7 patients (57%) were bacteremic. The diagnosis was made by computerized tomographic (CT) scan or ultrasound in 6 cases and at autopsy in 1 case.

Bacterial pneumonias: There were 15 episodes of bacterial pneumonia in 14 patients, 3 of whom were men and 11, women. Six (40%) of the episodes had a fatal outcome. Of the 15 episodes, 10 were nosocomial and 5 were community-acquired pneumonias. Only 2 (13%) of the pneumonias were associated with bacteremia. Seven episodes (70%) of nosocomial pneumonias occurred while the patient was intubated. Aspiration was documented in the other 3 episodes of nosocomial pneumonia, and they were diagnosed within the first week after transplantation. One episode of nosocomial pneumonia was caused by *S. aureus* and the remainder were caused by aerobic gram-negative bacteria: *Pseudomonas aeruginosa* (4 episodes), *Enterobacter cloacae* (2 episodes), *E. aerogenes* (2 episodes), *P. maltophilia* (1 episode) and *Acinetobacter* (1 episode). The community-acquired pneumonias were due to *S. aureus* (2 episodes), *Pneumococcus* (2 episodes) and *Escherichia coli* (1 episode). Respiratory secretions for cultures were obtained either by suction of deep tracheal secretions (7 patients), bronchoscopy (4 patients or expectorated sputum (4 patients).

Soft-tissue infections: There were 10 episodes of soft-tissue infection in 9 patients. Only 3 episodes were associated with bacteremia. Two of these episodes occurred in 1 patient and were associated with his

death. This patient developed a *Streptococcus fecium* abdominal wound infection 16 days after transplantation; 13 days later an abdominal wall abscess with *Klebsiella pneumonia* and *Citrobacter freundii* occurred at the same site.

The onset of soft-tissue infection varied from 6 days to 230 days after transplant surgery but in 8 of 10 episodes it occurred within the first month after transplantation. Eight cases were infections of the abdominal wound or abscesses in the abdominal wall near an abdominal wound. The other 2 cases were an infected hematoma of the leg and a perirectal abscess. The organisms involved were: gram-negative aerobes (3 cases), gram-positive aerobes (2 cases), and mixed flora (5 cases).

Cholangitis: There were 9 well-defined episodes of cholangitis in 6 patients. Eight of 9 episodes were associated with technical surgical problems: biliary duct strictures (5 patients), complicated surgery requiring vascular grafts (2 patients), and biliary leak (1 patient). A temperature elevation was present during all 9 episodes (37.7 °C–40 °C) but only 4 (44%) of the 9 episodes were associated with bacteremia. The organisms involved were: aerobic gram-negative rods (2 episodes); aerobic gram-positive cocci (2 episodes); anaerobes (1 episode); multiple organisms (4 episodes). The 4 bacteremic episodes were due to *K. pneumonia, S. fecalis, B. fragilis* and *P. aeruginosa* together with *S. fecalis.*

One patient with biliary duct strictures had 4 recurrent episodes of cholangitis. The shortest onset of cholangitis was 3 days after very difficult surgery and the longest onset was 552 days after transplant surgery in a patient with biliary duct strictures. Three episodes of cholangitis were associated with death (33%).

Peritonitis: Nine episodes of peritonitis occurred in the series. Six were due to bacteria (gram-negative aerobic, 2; gram-positive aerobic cocci, 3; anaerobe, 1) and 3 to *Candida* species. Two bacterial episodes were associated with bacteremia. Although 7 episodes were associated with temperature elevations between 37.6 °C and 40 °C, 2 patients with *Candida* infection did not have fever. Five episodes were related to biliary leaks. One of these occurred after extraction of a t-tube and another followed a t-tube cholangiogram. The other cases were associated with hepatic artery thrombosis (2 cases) and colonic perforation (1 case). Three (33%) of the 9 episodes of peritonitis were associated with death.

Bacteremias: Thirty-three bacteremias occurred in 26 patients, including 13 women and 13 men. Twelve of the bacteremias (36%) had a fatal outcome. The mean onset was 132 days after transplantation and the range was 5 to 552 days. The most common source was the abdomen (33%), followed by the urinary tract (21%). The other bacteremias with a known source arose from wound infection (9%), intravenous catheters (6%), pneumonia (6%), and endocarditis (3%). Twenty-one percent of the bacteremias did not have a known source. It is likely that most of these originated in the abdomen. Fifty-one percent of the blood cultures with single isolates were gram-negative aerobic bacteria, 27% were gram-positive aerobic organisms, and 9% were anaerobes. Twelve percent of positive cultures had multiple isolates.

CMV disease: Symptomatic CMV occurred in 22 patients (22%) in this series. These patients included 15 cases of CMV viral syndromes, 6 cases of disseminated disease and 1 case of isolated CMV hepatitis. Of these 22 patients, 10 were males and 12 females. Their mean age was 39 years and the mean onset was 37 days after transplantation (range, 16–149 days). Twenty-one of 22 episodes occurred within 7 weeks of a transplant operation.

The most common presentation of CMV disease was fever with neutropenia and atypical lymphocytosis (14 patients). Eleven patients (50%) had both neutropenia and thrombocytopenia. The mean duration of fever was 13 days (range, 7–24). The patient who developed CMV hepatitis had a temperature elevation over 40 °C for 12 days and 22% atypical lymphocytes on her peripheral blood smear.

Five of 6 patients with disseminated disease were diagnosed at autopsy. Their disease involved multiple organs, including both the liver and lung in 5 patients. Four of these patients developed a picture of "adult respiratory distress syndrome" on chest radiograph and required intubation and high end expiratory pressure for ventilation. The 1 patient with disseminated CMV who survived had hepatitis and gastritis but did not develop CMV pneumonitis. All 6 patients with disseminated disease had received OKT3 therapy as treatment for rejection.

Herpes simplex infections: Thirty-five of the 101 liver transplant recipients (34%) had herpes simplex (HSV) infections. Of these, 32 patients had non-severe mucocutaneous disease. Twenty-three patients had isolated oral herpes simplex infection; 7 patients had isolated genital herpes infection; 1 patient had infection of both the genitals and the skin of a lower extremity; and 1 patient had herpes stomatitis, genital herpes, and herpes keratitis at different times.

Three patients had severe visceral herpetic infections (Table 3). These included a case of disseminated HSV infection in multiple organs, 1 case of isolated HSV infection of a third hepatic allograft and 1 case of HSV esophagitis and colitis. These 3 cases were diagnosed at postmortem examination. Fifty percent of herpetic infections occurred within 3 weeks after a transplant operation. Most patients with non-

severe HSV infections were treated with oral or intravenous acyclovir and all their infections healed. All 3 patients with visceral disease died.

Varicella-zoster: There were 5 cases of herpes zoster infections (5%), 4 of them with only localized skin manifestations. Their range of onset was 116 to 551 days. The fifth case had disseminated varicella with viremia and hepatitis, and infection occurred 28 days after transplantation.

Candida infections: There were 14 invasive *Candida* infections in 13 patients. All occurred within 2 months of a liver transplant operation. The latest infection was 183 days after the original transplantation, but only 4 days after a third allograft was placed.

Of the 13 patients, 7 had histological evidence of candidal tissue invasion. Five of these patients had disseminated disease, 1 had invasive esophagitis, and 1 had necrotizing cystitis with invasion of *Candida* into the bladder muscle. The other cases were diagnosed either by isolation of *Candida* from the blood stream (3 patients) or by isolation of *Candida* at laparotomy from peritonitis or an intra-abdominal abscess (3 patients).

The species of *Candida* isolates were *C. albicans* (10 isolates), *C. glabrata* (3 isolates) and *C. tropicalis* (1 isolate).

Ten of the patients with invasive candidiasis (77%) died. In 4 of these patients the diagnosis was not suspected before death and established only at postmortem examination.

Nine patients received amphotericin B for an average of 18 days (range, 7–40). The 3 patients who survived included 2 patients with candidemia and 1 with *Candida* peritonitis.

Deaths in these patients were not always uniquely due to *Candida* infection, as 11 of the patients with *Candida* infection also had either severe bacterial infections and/or viral infections during follow-up.

Aspergillosis: There were 4 patients with systemic *Aspergillus* infections in this series; all of these infections were fatal. The sites of involvement were in the lung alone (1 patient), the heart, stomach and liver (1 patient) and the lung and brain (2 patients). All but 1 patient had a postmortem examination. Three patients were suspected to have fungal infection during life and were treated with 9 to 24 days of amphotericin B. One patient was not treated and on postmortem examination was found to have *Aspergillus* pneumonia.

Pneumocystis carinii pneumonia (PCP): Eleven patients in this series, including 7 women and 4 men, had PCP infection. The mean onset was 89 days after liver transplantion (range, 20–140). Two cases that occurred quite early after transplantation (on days 20 and 37) differed from the cases that occurred later in that they presented with localized chest infiltrates and only a few organisms were found by methenamine silver stain of cells obtained by broncho-alveolar lavage. Nine cases occurred between 53 and 140 days after transplantation and presented with diffuse interstitial infiltrates. The symptoms at presentation were fever (100%), cough (45%), and shortness of breath (30%). All 11 patients were started initially on a regimen of trimethoprim-sulfamethoxazole, but 5 patients were treated later with pentamidine or a combination of pentamidine and trimethoprim-sulfamethoxazole because of persistent fever and hypoxia. There were 3 fatalities in the series and all 3 of them were complicated by CMV pneumonitis.

Toxoplasmosis: There was only 1 case of toxoplasmosis in this series. This was a 57-year-old woman who became confused 39 days after transplantation and developed lymphocytic meningitis. The diagnosis was made after the patient had recovered when *Toxoplasma gondii* was isolated in tissue culture of a buffy coat sample of her blood. This case has been reported in greater detail elsewhere (13).

Pretransplantation risk factors for infection

The frequencies of infection expressed as number

TABLE 4. Frequency of severe infections and mortality in relation to sex, age and underlying diagnosis

	Number	E/P	% Patients infected	% Patients died
I. Sex				
Males	39	1.31	64	28
Females	62	1.37	69	24
II. Age				
≤41 yr	52	1.25	61	19*
>41 yr	49	1.45	69	39*
III. Underlying Diagnosis†				
Cholestatic disease	51	1.20	61	24
Hepatocellular disease	35	1.46	74	31
Other	15	1.73	73	20

*P=0.06 by Fisher's Exact Test.
†See Table 1 for details of diagnosis.

of episodes of infection per patient and mortality related to demographic variables of sex, age, and underlying diagnosis are shown in Table 4. Infection frequencies and mortality rates did not differ for men or women or for patients older or younger than the median age, although there was a trend for mortality to be higher in patients older than 41 years ($p = 0.06$; Fisher's Exact Test).

When patients were allocated to diagnostic categories of hepatocellular disease (35 patients), cholestatic disease (51 patients) and miscellaneous liver diseases (15 patients), infection rates were noted to be slightly, but not significantly, lower in patients with cholestatic liver disease than in patients with other diagnoses. In addition, we did not find significantly higher or lower infection rates related to any common specific diagnosis such as chronic active hepatitis, primary biliary cirrhosis, or sclerosing cholangitis.

We attempted to define risk factors for infection by assessment of the effect of pretransplant clinical and laboratory variables. Eight discrete clinical variables in the pretransplant period were investigated for their possible association with infection (Table 5). The use of corticosteroids in the preceding month; the use of intravenous antibiotics in the preceding month; the presence of ascites, encephalopathy, a history of gastrointestinal bleeding; the presence of a thrombosed portal vein; the presence of a biliary drain; and a positive hepatitis B surface antigen test were not associated with a significantly higher or lower frequency of infection after transplantation.

Patient charts were investigated for 25 pretransplant laboratory studies ordered which might be associated with the frequencies of infection. Not all test results were available on all patients, but the mean number of results available was 21 per patient.

Twenty-five blood laboratory results were examined for their possible relationship with later infection frequencies including serum creatinine, total white blood cells count, polymorphonuclear cells, lymphocytes, platelets, hematocrit, T-helper/T-suppressor ratio, total T cells, T-helper lymphocyte count, T-suppressor lymphocyte count, total hemolytic complement (CH100), quantitative immunoglobulins (including IgG, IgM, and IgA), albumin, globulin, iron, ferritin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transferase, prothrombin time and partial thromboplastin time. Only 2 results showed a significant association with infection (Table 6). Patients with a T-helper/suppressor (H/S) ratio of ≤ 2.8 ($N=33$) had more episodes of severe infection (1.66 per patient vs. 0.85 per patient, $P<0.02$, t-test). Also, patients with ALT (SGPT) values > 60 IU/L had an infection frequency of 1.56 episodes ($N=50$), while patients with ALT values ≤ 60 ($N=48$) had an infection frequency of 0.97 episodes ($P<0.05$, t-test).

The analysis was further made for subcategories of bacterial, viral, fungal, and protozoal infections with respect to the above 2 laboratory tests. We found that patients with lower H/S ratios had significant higher frequencies of severe viral ($P<0.02$) and fungal ($P<0.01$), but not bacterial or protozoal, infection. Patients with higher levels of ALT, on the other hand, did not have higher infection frequencies in any specific pathogen category.

TABLE 5. Pretransplant clinical variables and frequency of severe infection after transplantation

Variable	No. with (E/P)	No. without (E/P)
Steroid use	17 (1.41)	84 (1.33)
Ascites	61 (1.26)	40 (1.47)
Gastrointestinal bleeding	52 (1.44)	49 (1.24)
Encephalopathy	37 (1.21)	64 (1.42)
Biliary drain	8 (1.25)	93 (1.35)
Thrombosed portal vein	8 (0.62)	93 (1.40)
Antibiotics i.v.	15 (1.46)	86 (1.32)
Positive HBsAg	7 (2.0)	94 (1.29)

Surgical risk factors for infection

Table 7 shows the surgical procedures performed on 101 liver transplant recipients. There were a total of 127 transplant operations and 69 other operations.

As shown, 80 patients had a single transplant operation. The reasons for retransplantation included: primary liver failure (11 cases); technical problems (7 cases) including 5 cases of hepatic-artery thrombosis, 1 case of aortic graft thrombosis and 1 case of hepatic artery stenosis: rejection (6 cases); and infection (2 cases). One infected patient had recurrent fulminant hepatitis B of the transplanted liver and the other had bacterial liver abscesses refractory to antibiotic therapy.

Figure 2 shows the rate of severe infections in relation to total surgical time. For this analysis time spent in the operating room for drainage of abscesses was excluded. As shown the infection rates rose steadily with increasing surgical time. The overall infection frequency in patients who spent more than

TABLE 6. Correlation of pretransplant laboratory values with infections after transplantation

Lab. Variable	No. Pts. tested	Median value	Pts. > Median	E/P	Pts. ≤ Median	E/P	P
T-helper/T-suppressor ratio	61	2.8	28	0.85	33	1.66	<0.02
ALT (SGPT)*	98	60 IU/L	50	1.56	48	0.97	<0.05

*ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase)

TABLE 7. Summary of 196 surgical procedures in 101 liver transplant recipients

Transplant operations (127 operations)
One transplant operation (80 x 1 = 80)
Two transplant operations (16 x 2 = 32)
Three transplant operations (5 x 3 = 15)
Other operations (69 operations)
Drainage of abdominal abscesses (16)
Treatment of intra-abdominal bleeding (15)
Repair of biliary leaks (11)
Laparotomies with no findings (5)
Tracheostomies (5)
Repair of biliary strictures (4)
Treatment of gastrointestinal bleeding (3)
Others (10)

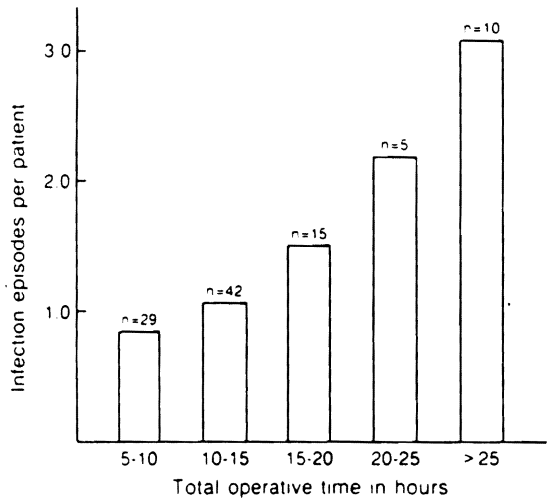

FIG. 2. Frequency of severe infections in relation to total operative time per patient in hours.

12 hours in the operating room was 1.97 episodes/patient (E/P) versus a frequency of 0.97 infections per patient in those who spent less than 12 hours in the operating room ($p < 0.001$). Also patients with more than 1 abdominal operation had a higher infection frequency compared to those who had only 1 transplant operation and no other laparotomies (1.95 E/P vs. 0.86 E/P, $P < 0.001$).

The rates of severe infections with different pathogen types for patients who spent more or less than 12 hours (the median) in the operating room was also analyzed. Significant differences were noted for severe bacterial infections ($P < 0.01$), severe fungal infections (< 0.001), and severe viral infections ($P < 0.05$). Remarkably, all 18 severe fungal infections occurred in patients who spent more than 12 hours in the operating room.

Table 8 shows frequencies (E/P) of severe infections, in relation to the type of biliary drainage. The groups analyzed were 65 patients who had only a choledocho-choledochostomy with t-tube placement (CC) and 36 patients who had a choledocho-jejunostomy (CJ) performed either at the initial transplantation or later. The analysis is further broken down into patients who had only 1 transplant operation and those who had more than 1 transplant operation. Patients who had only 1 transplant operation had very similar frequency of infection whether they had a CC or a CJ. By contrast, the patients who had more than 1 transplant operation had a higher frequency of infection if a CJ was employed (3.25 vs. 1.50 E/P, $P < 0.02$). This was then reflected in an overall higher frequency of infections in patients with CJ compared to those with CC (1.72 vs. 1.14 E/P, $P < 0.05$).

The 11 patients who underwent more than 1 transplant operation and had biliary drainage via a CJ had a very high mortality rate (10/11 = 91%). These 11 patients had a total of 27 transplant operations. Four of the patients had only CJs and 7 patients had an original transplantation employing a t-tube but were switched to CJ later.

Non-surgical risk factors for infection

The frequency of severe infections by various pathogens was analyzed in relation to the use of additional immunosuppressive agents and steroids. The factors analyzed were the use of OKT3, the use of azathioprine for more than 7 days, and the administration of greater than 5 (the median number) of recycles or boluses of steroids. For the purpose of analysis a steroid bolus was considered to be equivalent to a steroid recycle. There was no significant association between the use of azathioprine or frequent steroids and higher frequencies of infection (1.32 E/P vs. 1.37 E/P for azathioprine, and 1.55 E/P vs. 1.21 E/P for steroids). The only significant result was that patients given OKT3 had a higher frequency of protozoal infections ($P < 0.05$). We could not demonstrate a higher frequency of severe viral infections in patients receiving OKT3 (0.27 E/P vs. 0.23 E/P). However, when we analyzed all viral infections together (severe and non-severe), we did find that patients on OKT3 had higher frequency of viral infections than patients not receiving OKT3 (0.76 E/P vs. 0.46 E/P, $P < 0.05$, t-test).

The frequencies of infection were analyzed in rela-

TABLE 8. Severe infections in relation to type of biliary drainage

	Drainage Procedure		
	CC*	CC, CJ†	P
Pts. with 1 Tx	55	25	
Frequency of infection (E/P)	1.07	1.04	$P > 0.05$
Pts. with more than 1 Tx	10	11	
Frequency of infection (E/P)	1.50	3.27	$P < 0.02$
All patients	65	36	
Frequency of infection (E/P)	1.14	1.72	$P < 0.05$

Abbreviations: Tx = transplantation, CC = chodedocho-choledochostomy, CJ = choledocho-jejunostomy.
*Patients with CC with t-tube only.
†Patients with CJ or patients who started with CC but then were converted to CJ.

TABLE 9. Blood products and severe infections after liver transplantation

Blood Product	Median units/pt	No. pts. > median	E P	No. pts. ≤ Median	E/P	P
RBC	25	51	1.66	50	1.02	<0.02
FFP	30	51	1.66	50	1.02	<0.02
PLT	29	52	1.51	49	1.16	NS
Cryo	6	45	1.55	56	1.17	NS

Abbreviations: RBC = red blood cells, FFP = fresh frozen plasma, PLT = platelets, Cryo = cryoprecipitate, NS = not significant.

tion to high or low mean levels of CyA. For each patient a monthly mean was calculated of 4 weekly median CyA levels. Average CyA levels for all patients were 1002 ng/ml (range, 519–1855) in the first month, 1046 ng/ml (range, 257–2068) in the second month, and 946 ng/ml (range, 190–1720) in the third month after transplantation. Oddly, we could not document higher rates of infections in patients who had higher levels of CyA. On the contrary, we found a significantly higher overall frequency of infections in patients who had *lower* levels of cyclosporine during the second post-transplant month. This appeared to be related to lowering of the cyclosporine dosage in patients who were already infected during the first post-transplant month, because further analysis showed that the patients with lower CyA level in the second month had higher infection rates only in the first month ($P < 0.001$), not in the second or third months.

To assess the impact of antibiotics on infection rates, we counted the number of days of treatment with non-prophylactic additional intravenous antibiotics in the first 3 months after transplant operation. Sixty-five patients received additional intravenous antibiotics in this time period and 36 patients received no additional antibiotics. Overall, the average duration of additional antibiotic administration was 9 days, and the median was 5 days. Patients who received higher than the median days of intravenous antibiotics had higher rates of severe infections (2.02 E/P vs. 0.68 E/P, $P < 0.001$, t-test). When different pathogen groups were analyzed, this relation held for both severe bacterial and severe fungal infection ($P < 0.001$), but not for severe viral or protozoal infections. All 18 severe fungal infections in this series occurred in patients who received more than 5 additional days of intravenous antibiotics.

We correlated infection frequencies with the number of units of different blood products received by the patients. The results are shown in Table 9. This analysis shows that patients who received more than the median units of red blood cells (RBC) and fresh frozen plasma (FFP) had higher post-transplant infection frequencies ($P < 0.02$ for both RBC and FFP). This was not shown with platelets and cryoprecipitate. When severe infections were broken down to specific pathogens, we found that patients who received more RBC and FFP had higher rates of only bacterial infections ($P < 0.02$) and fungal infections ($P < 0.01$), but not viral or protozoal infections.

Discussion

Liver transplantation has now become an acceptable mode of treatment for end-stage liver disease. A number of previous publications, including studies from our own institution, have described one or another aspect of infections after liver transplantation (7, 8, 17, 27). There has been, however, no comprehensive study of infections in liver recipients on cyclosporine. In this study we attempted to provide a thorough description of the epidemiology and risk factors for all types of infections in a sizable adult liver transplant population.

A comparison of the results in this study with our previous study, covering 1981 to 1983 (11), shows that although the overall percentage of infected patients (83% vs. 81%) was similar, the number of deaths associated with infection was significantly lower in the present study (23/101 = 23% vs. 17/43 = 40%, $P < 0.05$). The reasons for the decline in infectious mortality are not known but are probably related to technical advances in surgery (such as introduction of veno-venous bypass during transplantation) and to other improvements in patient management (such as the monitoring of cyclosporine levels after transplantation).

In our study the critical period for infections was the first 2 months after transplantation. Seventy percent of all severe infections and 93% of severe viral and fungal infections occurred during this period. The few severe viral and fungal infections that occurred later followed retransplantation.

By contrast, 94% (16/17) of infections occurring later than 6 months after transplantation were bacterial. Most of these were routine infections like pneumonia, urinary tract infection and cholangitis, infections that may be seen in a non-immunosuppressed surgical population. *Pneumocystis* infections occurred throughout the first 6 months after transplantation but were not diagnosed thereafter.

High rates of fungal infection were first documented by Schroter et al (18) in liver recipients receiving azathioprine and prednisone. We found a 42% incidence of fungal infection in adult liver recipients receiving CyA and prednisone between 1981 and 1983 (27). Significant associations with the occurrence of fungal infections in that series were the pre- and post- transplant use of corticosteroids and antibiotics, and the length of surgery. We also found previously that patients with a diagnosis of primary

biliary cirrhosis had significantly fewer fungal infections and a lower death rate.

The present series shows that severe fungal infections are still a serious clinical problem (16% in this series) and lead to high mortality (13/16 = 81%). However, the decline in incidence of fungal infections from the previous series is highly significant ($P < 0.001$) and probably represents the most important improvement in mortality due to infections in our liver transplant recipients.

In this series, the pretransplant use of antibiotics and pre- and post-transplant use of steroids were not found to be significant risk factors for fungal infection, but there continued to be very strong associations between the occurrence of severe fungal infections and an increased use of post-transplant antibiotics and prolonged operative time. As in previous studies of liver transplant recipients, the important fungal pathogens were *Candida* and *Aspergillus* and all such infections occurred in hospitalized patients.

Although a few cryptococcal infections have occurred in our liver transplant population, they were not seen in this series and appear to occur in 1% or less of liver recipients in the first year after transplantation.

The reason for the decline in the rate of fungal infection in the present series is unknown but may relate to better operative techniques, more judicious use of antibiotics, and better control of immunosuppression—or greater willingness to institute empiric amphotericin B therapy in high-risk patients. The strong association found here between severe fungal infections and prolonged surgery might form the basis for future investigations of antifungal prophylaxis in patients with prolonged operative time.

Eleven of 33 bacteremias (33.3%) in this series originated in the abdomen. Many bacteremias without known source probably also originated in the abdomen. Like fungal infections, early bacterial abdominal infections (abdominal and liver abscesses, peritonitis, cholangitis) were associated with prolonged surgical time and increased number of abdominal operations. Only about 50% of the patients in this series had a single abdominal operation. The common reasons patients returned to the operating room were for retransplantation or abdominal explorations for bleeding, biliary leak, and biliary stricture. Biliary complications and other technical problems are highly associated with infections after liver transplantation (14, 15, 25). Hepatic artery thrombosis is a particularly serious technical complication occurring in 3.4% of adults. It may lead to infectious complications such as cholangitis, infected bile collections, and liver abscesses, and often culminates in retransplantation (26). The bacterial pathogens encountered were those typically seen in hospitalized surgical patients with a predominance of gram-negative enteric rods.

Eight of the 101 patients (8%) developed infection of the abdominal wound by our criteria. This rate is quite similar to the rates of wound infection after elective biliary tract surgery (6) or other clean-contaminated operations (5). It should be noted that in order to use clear-cut criteria we only included cases in which incision and drainage or surgical debridement were employed. Thus, our rate should be considered a minimal estimate of the rate of wound infection after liver transplantation. Minor degrees of erythema at the surgical wound are quite difficult to evaluate in these patients and although these often prompted antibiotic therapy, their clinical significance is unclear.

Symptomatic cytomegalovirus infections were the most common severe infection after liver transplantation (22 episodes). Six patients in the series had disseminated CMV and 5 (83%) of them died. Although our analysis did not demonstrate an association between symptomatic CMV infection and use of OKT3, azathioprine, or large numbers of steroid boluses or recycles, all 6 patients with disseminated CMV had received OKT3. Anti-T-cell globulins have been previously shown to be a risk factor for severe CMV infections (2, 10, 16). Mucocutaneous herpes simplex virus infections, classified as a non-severe infection, were quite common (32% of our population), and were easily managed with antiviral therapy, but there were also 3 cases of visceral HSV infection that were diagnosed only at postmortem examination.

Pneumocystis carinii pneumonia occurred in 11 patients (11%) in this series. This rate of *Pneumocystis* infection is similar to that found in other studies of transplant recipients (9, 12). The significantly higher rate of protozoal infections in patients receiving OKT3 suggests that patients in this group might be candidates for prophylaxis with trimethoprim-sulfamethoxazole. Interestingly, the 3 patients who did not recover from their pneumonia had complicating CMV disease in the lungs. Clinicians should be aware that other infections, particularly CMV infection, may accompany *Pneumocystis* pneumonia and be a cause for a poor response to therapy.

We could not document any definite association between demographic variables of sex, age, or pretransplant diagnosis and infection rates, although there was a trend toward higher mortality rate in older recipients. There also appeared to be a trend in favor of lower infection rates in patients with cholestatic disease and it is possible that studying a larger group would have shown a significant difference.

Eight pretransplant clinical variables and 25 pretransplant laboratory values were investigated to see if these were associated with higher frequencies

of infection. The only 2 pretransplant variables associated with higher rate of infection were lower T-helper/T-suppressor (H/S) ratio, and higher ALT levels before transplantation. The finding of higher ALT in association with higher rate of severe infections is consistent with our finding that patients with hepatocellular disease do somewhat worse than other patients (27). When we analyzed H/S ratios in various infection types, we found that lower pretransplant rates were associated with higher rates of severe viral ($P < 0.02$) and severe fungal infection ($P < 0.01$), but not bacterial or protozoal infections. Oddly, we found no correlation between the absolute number of T-helper cells or T-suppressor cells and the incidence of infection, suggesting that the balance of helper and suppressor cells was more important than the absolute numbers. The impact of pretransplant immune status on post-transplant infections is poorly understood and requires further study, but such a study might be clinically helpful in deciding how intensively to apply pharmacological immunosuppression.

Of all the factors influencing the rate of infections after liver transplantion, surgical factors appear to be the most important. Other authors have shown correlations between operative time and postoperative rate of infection. Shapiro et al (19) showed that higher risk of infection after hysterectomy was associated with increased surgical time, and Cruse and Foord (5) showed a direct relation between length of surgery and infection of surgical wounds.

In our series we found that more prolonged surgical time and increased number of abdominal operations were both strongly associated with more bacterial and fungal infections. The most striking finding was the fact that all severe fungal infections occurred in patients with more than 12 hours (the median) of operative time.

Another surgical factor we found to be important in infections after the transplant operation was the type of biliary drainage. Although the type of drainage system did not influence the rate of infection (1.07 vs. 1.04) in patients who underwent only 1 transplant operation, patients who had more than 1 transplant operation had a higher frequency of infection if a choledocho-jejunostomy was performed. There are 2 possible explanations for this finding. The most likely is that patients who require conversion to Roux-en-Y or repeat Roux-en-Y are intrinsically a higher risk group. However, the finding may also reflect a higher risk of surgical entry into the bowel in the post-transplant period, when it is more likely to be colonized with antibiotic-resistant bacteria and *Candida*. While the choice of drainage procedure is generally determined by the technical surgical situation, it is still useful to recognize that repeat CJ is a very high-risk situation.

In the analysis of severe infections in relation to immunosuppression (excess steroids, OKT3, azathioprine), the only significant finding was in patients who received OKT3 therapy. While we could not show that the overall frequency of infection was increased by OKT3, protozoal (*Pneumocystis*) infections and all viral infections (both severe and nonsevere), were more common. Monoclonal antibodies including OKT3 provide powerful means to treat rejection (4), but their impact on infection remains to be comprehensively studied.

Serious infections compromise the course of many patients after liver transplantation. We have shown a historical decline in infectious mortality when comparing our current results with previous studies. It is likely that infections will be reduced even further as technical advances are made in the transplant operation, and better noninvasive tools are developed to diagnose abdominal infections.

Fungal infections are still a serious clinical problem. Early diagnosis of *Candida* and *Aspergillus* infections by serological methods still needs further study (1). Over the years we are moving to earlier empiric treatment of liver transplant recipients at high risk for fungal infections, before a definitive diagnosis is made. This study further defines particular risks for fungal infection, especially prolonged surgery and prolonged antibacterial treatment that could form the basis for trials of prophylactic antifungal therapy. Unfortunately, the only reliable drug now available for the treatment of invasive candidiasis or aspergillosis is amphotericin B. Effective and less toxic alternative antifungal agents are needed.

Summary

We studied infections in 101 consecutive patients who underwent liver transplantation between July 1984 and September 1985. The mean length of follow-up was 394 days. Eighty-three percent of the population had 1 or more episodes of infection and 67% of the population had severe infections. The overall mortality was 26/101 (26%) and 23 of 26 deaths (88%) were associated with infection. Seventy percent of severe infections occurred in the first 2 months after transplantation.

The most frequent severe infections were abdominal abscess, bacterial pneumonia, invasive candidiasis, *Pneumocystis* pneumonia, and symptomatic cytomegalovirus infection. Patients with more than 12 hours of cumulative surgical time had a higher rate of severe infections ($P < 0.001$), particularly fungal ($P < 0.001$) and bacterial ($P < 0.01$) infections. Also, the use of choledocho-jejunostomy was associated with a higher rate of infection in patients who had more than 1 transplant operation ($P < 0.02$). No increase in infection was found in patients who

received azathioprine, or more than the median number of steroid boluses or "recycles"; but patients who received OKT3 therapy had a higher rate of protozoal infections ($P < 0.05$). A result similar to that of our previous studies was a strong relation between the number of severe fungal infections and prolonged courses of antibiotics after transplant operation ($P < 0.001$).

Pretransplant manifestations of severe liver disease such as ascites, encephalopathy, and gastrointestinal bleeding were not associated with higher rates of infection after transplantation, but high serum levels of ALT were. Patients with lower ratios of T-helper to T-suppressor lymphocytes had more severe viral ($P < 0.02$) and fungal ($P < 0.01$) infections after transplantation.

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