

Infection and rejection in liver transplant patients: a 10-year Swiss single-centre experience

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Summary

Introduction: Graft rejection and infection remain major morbidities following orthotopic liver transplantation (OLT). Rejection treatment may be associated with an increased rate of infectious complications. The aim of this study was to determine the relationship between rejection, rejection therapy and the risk of associated infections.

Materials and methods: A retrospective study of all adult patients undergoing OLT between July 1987 and July 1997 at a single university medical centre was carried out. Data for all transplant recipients were collected using predetermined definitions for infectious complications.

Results: One hundred OLTs were performed on 98 patients (two patients received a second transplant). The cohort consisted of 33 women and 65 men with a mean age of 47 years. Seventy-eight patients developed a total of 228 infectious episodes: 107 bacterial, 101 viral, 17 fungal and

3 protozoan. The majority of infections occurred within the first month of OLT. Thirty patients without rejection developed 42 infectious episodes, whereas 70 patients with at least one treated rejection episode developed 186 infectious episodes. The overall rate of infection was 44.4 episodes per 1000 patient-days in the 30 days before rejection, and 94.4 episodes per 1000 patient-days in the 30 days following rejection treatment.

Conclusions: Infections occurred more frequently during the first month post-transplantation. Following OLT, rejection is associated with a higher incidence of infection, mainly of viral origin, concurrent with increased immunosuppressive therapy.

Key words: liver transplantation; acute rejection; infection; candidaemia; viral; bacterial; fungal infections

Introduction

Rejection and infection remain major causes of morbidity after liver transplant and account for up to 85% of deaths [1-5]. Unsuccessfully treated rejection results in graft failure and retransplantation [6], but the delicate balance between optimal immunosuppression to prevent rejection and excessive immunosuppression with the inherent risk of infection is difficult to achieve. Clinical studies have reported a correlation between the incidence and severity of infectious complications and anti-rejection therapy [1, 2, 7]. During a rejection episode, immunosuppression is supplemented either by increasing steroid doses or by adding an anti-T-lymphocyte drug. Both therapies are known to increase susceptibility to infection [1-4].

The objectives of the present investigation were to analyse the incidence and type of infection following orthotopic liver transplantation (OLT)

in adults, and to examine the temporal relationship between infection and rejection. This investigation was done in a single institution with the largest series of OLT in Switzerland.

Abbreviations:

ALS	anti-T-lymphocyte serum
CMV	cytomegalovirus
EBV	Epstein-Barr virus
HB Ag	hepatitis B antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HSV	herpes simplex virus
OLT	orthotopic liver transplantation
SDD	selective digestive decontamination

1 All the authors have contributed to a similar extent to the present manuscript.

The authors have no competing interests of any kind to declare for the present study, for which no financial support was received.

Material and methods

Study population and data collection

The University of Geneva Hospitals is a 1200-bed tertiary medical centre with approximately 40,000 patients admitted annually. Ninety-eight consecutive adult recipients of 100 orthotopic liver transplants from July 1987 to July 1997 were admitted to this retrospective study. Two patients were retransplanted. The cohort consisted of 33 women and 65 men with a mean age of 47 years (range 17–69 years). Clinical and transplant-related information was collected prospectively for each patient.

Immunosuppressive therapy

All patients received a uniform triple immunosuppressive regimen with methylprednisolone, cyclosporine and azathioprine. Methylprednisolone (1 g i.v.) was given intraoperatively, followed by 500 mg i.v. on the first post-operative day, and tapered gradually over 10 days to 10–20 mg/day, followed by oral prednisone (0.2–0.4 mg/kg per day). Cyclosporine (3 mg/kg per day i.v.) was started on day 0, and then administered orally to obtain cyclosporinaemia of 300 ng/ml (FPI monoclonal immunoassay). Azathioprine (2 mg/kg per day i.v.) was given for the first 2 weeks following transplant in a decreased dosage (1 mg/kg per day) for the following 2 weeks, given orally. Azathioprine was withdrawn if leukopenia developed (granulocyte count below 2800/mm³). Ganciclovir was administered as prophylactic therapy in patients seronegative for cytomegalovirus (CMV)-related infection but donor positive.

Rejection diagnosis and treatment

Acute rejection episodes were diagnosed by clinical and biochemical signs and confirmed by fine needle liver core biopsy [6]. Treatment consisted of methylprednisolone (1 g i.v., 1–3 injections) with or without steroid recycling. Steroid-resistant rejection was treated with either rabbit anti-T-lymphocyte serum (ALS; 3–5 g/kg per day) or orthoclone OKT3 (Muromonabun-CD3[®], Micromedex Inc, Greenwood Village, CO; 0.07 µg/kg per day) in the absence of thrombocytopenia and leukopenia. When necessary, these treatments were repeated. Rejection treatment often included a change from cyclosporine to FK506 (Prograf[®], Fujisawa Inc, Deerfield, IL). For the purpose of the study, a rejection episode was defined as any clinical event meeting all the above criteria. Any rejection treatment administered within 14 days of rejection was considered to be treatment of a single episode.

Perioperative antimicrobial prophylaxis

Perioperative antibiotic prophylaxis consisted of cefuroxime (1.5 g i.v. tid) given until removal of abdominal drainage, i.e. usually 4–6 days after surgery. Selective digestive decontamination of the oropharynx and the digestive tract was administered every 4 h (10–15 ml), starting after intubation and continuing for 10 days after transplantation. The regimen contained polymyxin B (150 mg), neomycin (1 g), and vancomycin (1 g) in 60 ml 5% dextrose. Nystatin (100,000 IU) was also administered simultaneously to prevent yeast colonisation.

Definition of infection

Microbiological surveillance cultures (respiratory secretions, blood, urine, bile, abdominal drainage fluids) were performed three times weekly; additional cultures were done when infection was suspected. At least two blood cultures were taken in the event of new unexplained fever (>38.5 °C). CMV culture, early antigen in blood and viraemia, early antigen in urine and sputum, were performed once weekly.

An infectious episode was defined as the association of compatible clinical signs and symptoms, laboratory tests and a microbial pathogen recovered from a normally sterile body site, followed by the introduction of an antimicrobial regimen directed against the microorganism identified. Recurrence of hepatitis C or B was also recorded. The diagnosis of bloodstream infection required the presence of the clinical signs of sepsis and isolation of microorganisms such as *Staphylococcus aureus*, gram-negative bacteria, or *Candida* species in at least one blood culture. For other pathogens, at least two positive blood cultures, or one positive blood culture associated with a documented primary infection site, were required [8].

A diagnosis of *cholangitis* was based on the existence of fever, right upper quadrant pain and/or abnormal liver function tests, with evidence of cholangitis on liver biopsy or isolation of the same microorganism in the blood and the choledochal T-tube drain. A diagnosis of *peritonitis* required clinical signs, the presence of leukocytes (>100 white blood cells per high power field), and positive cultures in peritoneal fluid obtained by percutaneous drainage or during surgery. An abscess was defined as a localised collection of purulent fluid, with typical clinical findings and positive microbiological cultures, confirmed by computerised tomography or laparotomy.

Pneumonia was diagnosed on the basis of clinical signs and symptoms (cough, dyspnoea, fever), the appearance of a new infiltrate on chest radiography and heavy growth of organisms in purulent tracheal secretions or bronchoalveolar lavage fluid ($\geq 10^4$ colony forming units/ml). These samples were examined after Gramstaining for the detection and quantification of leukocytes and organisms. The recovery of *Pneumocystis carinii* in bronchoalveolar lavage together with new infiltrates on chest radiography defined *P. carinii* pneumonia [5].

A diagnosis of *urinary tract infection* required the isolation of at least 10^4 microorganisms/ml once, or $\geq 10^5$ yeasts/ml twice, associated with at least two of the following: dysuria; pollakiuria; and/or pyuria (≥ 10 white blood cells per high power field).

Wound infection was diagnosed by clinical criteria and the isolation of microorganisms at least twice from surgery-related wounds.

Toxoplasmosis was diagnosed by seroconversion or by a significant rise (at least twice dilution) in specific antibodies [9].

A diagnosis of *fungus infection* was based on either: (a) positive blood culture; (b) isolation of fungi from an abdominal sample with evidence of peritonitis or an abdominal abscess; or (c) tissue invasion proven by biopsy [10].

Cytomegalovirus infection [11] was confirmed by seroconversion of CMV-specific IgG and IgM in a previously seronegative patient (primary infection), or by detection of a significant rise (more than four dilutions) in CMV IgG antibodies with or without detectable CMV IgM antibodies (secondary infection or reactivation). Leukocytes from peripheral blood co-cultured with human embryonic lung fibroblasts for 6 weeks and showing a cytopathogenic effect confirmed CMV infection in some cases.

CMV disease was diagnosed when CMV infection was temporally associated with: (a) gastroenteritis: upper or lower gastrointestinal symptoms with CMV detected in biopsy material from the gastrointestinal tract; (b) hepatitis: abnormal liver function tests in the absence of bacterial or fungal infection and/or transplant rejection, with CMV detected on liver biopsy by virological and/or histological techniques; (c) pneumonitis: pulmonary chest

symptoms and/or a typical chest radiographic pattern, lack of clinical response to antibiotics, and evidence of CMV in bronchoalveolar lavage fluids.

Herpes simplex virus (HSV) infection [12] was based on the presence of oral or genital serositis, and a positive viral culture or antigen detection by the indirect immunofluorescence technique for HSV. *Epstein-Barr virus* (EBV) infection [13] was diagnosed by seroconversion or by a significant rise in specific antibodies against EBV. HBV and HCV infections [14] were diagnosed by abnormal liver function tests, histological findings in liver biopsies associated with HB Ag, and HBV-DNA or anti-HBV antibodies in the blood.

Statistical analysis

For the purpose of this study, an infectious episode was defined as an independent event. If multiple infections were present on the same date, they were recorded as independent events only when diagnosed from different sources. The incidence of infection was defined as the number of infectious episodes per patient and per 1000 pa-

tient-days of care. The attack rate was defined as the number of infectious episodes occurring over a definite period of time. To assess the relationship between the occurrence of infection and rejection, we recorded the date at the start of rejection therapy, as well as the date of positive culture diagnosis, and the date of introduction of specific therapy. If a specific treatment was introduced before culture results were available, the date at the start of therapy was recorded. The rejection period was arbitrarily defined as a 60-day interval, from 30 days before to 30 days after rejection therapy. Patient characteristics and the outcome (infection and mortality) were compared using the chi-square test. Differences in the proportion of bacterial, viral, and fungal infections related to the number of rejection episodes, and the infection attack rates both before and after rejection therapy were computed using the Kruskal-Wallis test. Statistical analyses were performed using InStat® (GraphPad™ Software, Inc., CA, USA). All tests of significance were two-tailed and *p* values <0.05 were considered statistically significant.

Results

The most frequent preoperative diagnoses in our series were chronic viral-induced cirrhosis (48%) and primary biliary cirrhosis (17%) (table 1). Eighty-nine patients (89%) were followed for more than 1 year. The surveillance period averaged 64 months and represented a total of 531 patient-years. Nineteen patients died, representing a crude mortality rate of 19% at a follow-up of up to 64 months following transplantation (median 63 months); the 1-year mortality rate was 10%. Seven deaths (37%) were directly attributable to infection: five bacterial sepsis (*Escherichia coli* (2), *Proteus spp.*, *Streptococcus faecalis* and *Pseudomonas aeruginosa*); one fungaemia (*Candida tropicalis*); and one pulmonary legionellosis.

Incidence, timing, pathogens and infection sites

Seventy-eight (80%) of the 98 patients included in the study developed a total of 228 infectious episodes. One hundred and seven (47%) infectious episodes were due to bacteria (49 patients), 101 (44%) were viral (59 patients), 16 (7%) were due to fungi (14 patients), and three were due to protozoa (3 patients) (table 1). The overall incidence of infection was much higher during the first month following transplantation (figure 1): bacterial infection, 188.2 episodes vs. 5.8 (SD 260-8), *p* <0.0001; viral, 125.5 episodes vs. 9.5 (SD 243-10), *p* <0.0001; and fungal, 290.2 episodes vs. 8.8 (SD 346-6), *p* <0.0003 per 1000 patient-days (Mann-Whitney test). Three protozoal infections occurred and were diagnosed during the 4 months post-transplantation.

Of the 107 bacterial episodes, 94 were monomicrobial and 13 polymicrobial. The leading pathogens for the bacterial episodes were: *Enterococci* spp. (17 (16%) episodes), followed by *E. coli* (13 (12%) episodes), and coagulase-negative staphylococci (12 (11%) episodes). The blood-

stream was the leading infection site (39 episodes). The abdominal cavity was involved in 33 episodes of which 12 had concomitant bacteraemia (table 2). There were eight episodes of pneumonia with gram-negative rods; three were complicated by secondary bacteraemia. Gram-negative rods were recovered from 13 episodes of peritonitis with six secondary bacteraemias. Gram-positive cocci were responsible for 19 episodes of bacteraemia, six of which developed simultaneously to peritonitis; one was associated with intravenous catheter infection.

CMV infection accounted for 29% of all viral episodes. CMV disease occurred in six patients. There were 35 episodes of herpes virus infection of which 20 (57%) were due to *Herpes labialis*. Four episodes of HBV occurred in four patients, with recurrent disease in two. Of 37 patients with pre-transplantation hepatitis (C or C and B), 17 had recurrence of HCV.

Most fungal infections (88%) were caused by *Candida* spp. with *Candida albicans* as the leading fungal pathogen isolated (86%). *Candida glabrata* was responsible for one episode of peritonitis associated with liver infection. Seven abdominal fungal infections were observed. Most episodes of candidaemia (4/5) were secondary to an abdominal infection. One of two *Aspergillus* spp. infections caused a cerebral abscess.

One case of *Pneumocystis carinii* pneumonia occurred 81 days after transplantation and was associated with CMV pneumonitis. Three protozoan infections were identified but no death was attributable to such infections. Three episodes of toxoplasma seroconversion occurred 5, 87 and 120 days following transplant.

Rejection after liver transplantation

At least one biopsy-proven rejection episode occurred in 70% of transplant recipients. A single

Table 1

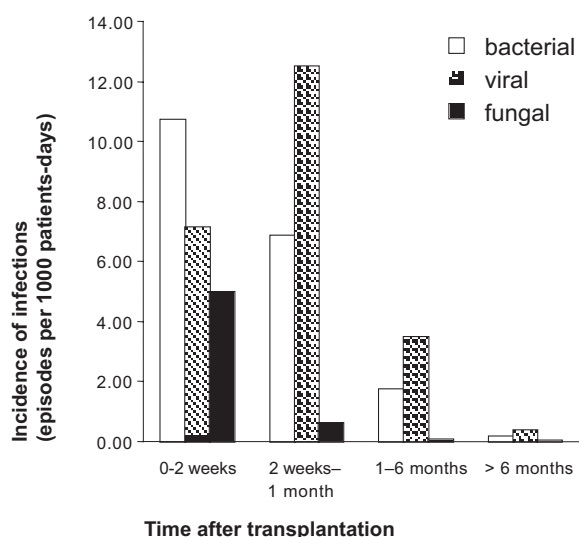
Pretransplantation diagnosis and cause of death.

Pretransplantation diagnosis	No. of patients	No. of OLTs	No. of deaths	Cause of death	Survival after OLT
<i>Advanced chronic liver diseases</i>					
Chronic viral-induced cirrhosis	48	48			
Hepatitis B virus (n = 16)			1	Cerebral oedema	6 months
			1	Sepsis+hepatitis B recurrence	12 months
			1	SAH	45 months
Hepatitis C virus (n = 28)			1	Primary non-functioning	5 days
			1	Pulmonary legionellosis	7 days
			1*	Rejection/infection and MOF	25 days
			1	Sepsis	4 months
			1	Sepsis	8 months
			1	Breast cancer with metastasis	27 months
			1	Chronic rejection	42 months
			1	Chronic rejection	67 months
Hepatitis B and C virus (n = 4)			1	ESLD post-hepatitis B recurrence	47 months
Primary biliary cirrhosis	17	17			
Primary sclerosing cholangitis	4	4			
Byler's disease	1	1			
Crigler-Najjar	1	1			
Alcoholic liver cirrhosis	9	9	1	Myocardial infarction post-operative endocarditis	36 months
Idiopathic autoimmune cirrhosis	4	4	1	Sepsis	3 months
			1	Rejection+ESLD	74 months
Amyloidosis	3	3			
Wilson's disease	2	2			
Alpha-1-antitrypsin deficiency	1	1			
<i>Hepatic malignancy</i>					
Hepatocarcinoma with: hepatitis B (n = 1), hepatitis C (n = 3)	4	4	1	Cerebral oedema	21 days
			1*	Malignant metastasis	12.5 months
<i>Fulminant hepatic failure</i>					
Fulminant hepatitis	4	4	1	Fungaemia	7.5 months
			1	Cerebral edema	28 months
<i>Retransplantation for chronic rejection</i>					
Total	98	100	19		

* Patients with associated hepatocarcinoma. OLT, orthotopic liver transplantation; SAH, sub-arachnoid haemorrhage; ESLD, end stage liver disease; MOF, multiple organ failure.

Figure 1

Incidence and timing of infection after liver transplantation. Bacterial (white bars), viral (hatched bars) and fungal (black bars) infectious episodes after liver transplantation ($p < 0.0001$), <30 days after transplantation compared to ≥ 30 days.



rejection episode occurred in 32 patients; two in 19 patients; three in nine patients; and more than three in ten patients. The median time between liver transplantation and the first rejection episode was 12 days (range 1–3705 days). Two patients underwent retransplantation for chronic rejection; one died of disseminated candidiasis and concomitant rejection. Of 70 patients with rejection, 36 (51%) were treated with high-dose steroids alone. Five patients were treated six times for steroid-resistant graft rejection with anti-lymphocyte T serum; three were switched to FK506 simultaneously. Fourteen patients received OKT3 and three were also switched to FK506 simultaneously.

Table 2

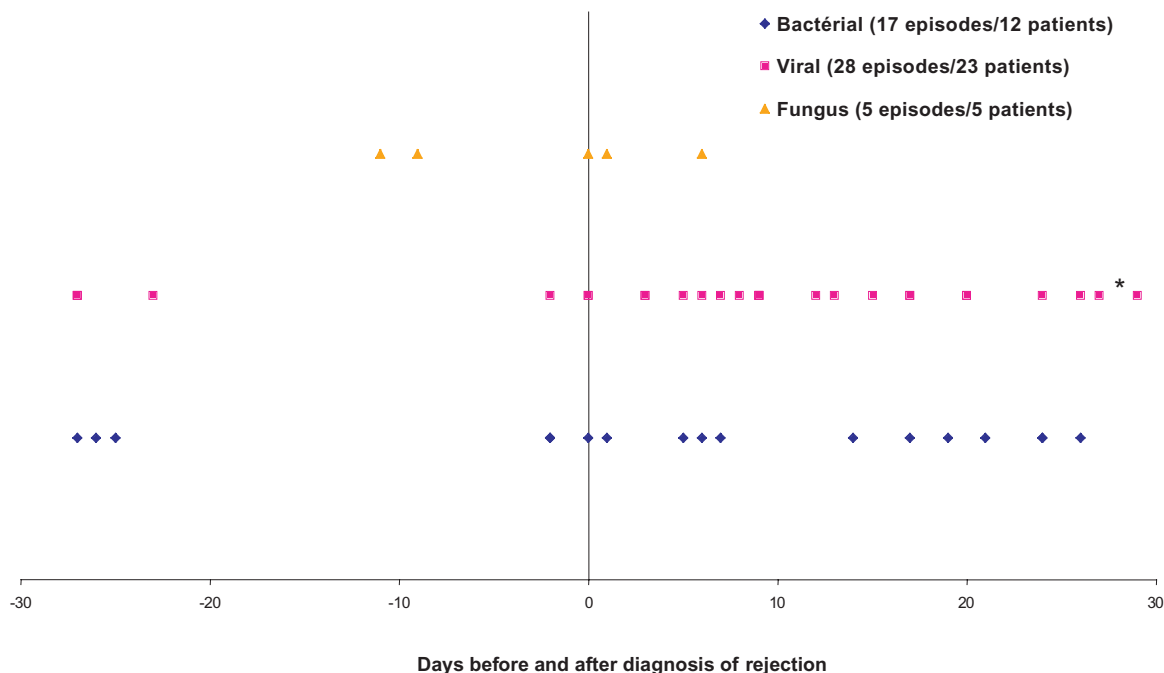
Distribution of bacterial, fungal and protozoan pathogens and infection sites among liver transplant patients

Pathogens	Peritoneum	Blood	Lung	Bile	Urine	Other
Bacteria						
Gram-positive						
Enterococci spp.	9	6		2	1	3
Staphylococci coagulase negative	5	9		4		4
<i>Streptococcus</i> spp.	4	3		5		2
<i>Staphylococcus aureus</i>						1
<i>Staphylococcus ludgenensis</i>		1				1
<i>Chlamydia</i> spp.					1	
Gram-negative						
<i>Escherichia coli</i>	1	5		5	8	1
<i>Klebsiella</i> spp.	3	6	1	2	1	3
<i>Pseudomonas aeruginosa</i>	2	2	4		1	
<i>Bacillus</i> spp.	2	1				
<i>Pseudomonas cepacia</i>	1		2			
Other gram-negatives*	6	6	1		3	4
Total bacteria	33	39	8	18	15	19
FUNGI						
Liver						
<i>Candida albicans</i>	6	5	4	3	4	2
Non- <i>Candida albicans</i> spp.	1			1		
<i>Aspergillus</i> spp.			1			1
<i>Pneumocystis carinii</i>			1			
Total fungi	7	5	6	4	4	3
PROTOZOA						
<i>Toxoplasma gondii</i>		3				1
Total protozoa		3	0			0

* Other gram-negatives include: *Aeromonas hydrophila*, *Enterobacter* spp., *Legionella pneumophila*, *Proteus mirabilis*, *Proteus vulgaris*, *Hafnia* spp., *Salmonella typhi*, *Morganella morganii*, *Campylobacter jejuni*.

Figure 2

Thirty-day relationship of new infection episodes both before and after rejection diagnosis. Infectious episodes reported in the 30-day period preceding or following a rejection episode treated with steroids: ♦, bacterial (17 episodes/12 patients); ■, viral (28 episodes/23 patients); ▲, fungal (5 episodes/5 patients).



Relationship between infection and rejection

Thirty transplant recipients without rejection developed 42 infectious episodes, whereas 70 recipients with at least one treated rejection episode developed 186 infectious episodes. The incidence of fungal infection correlates with the number of

rejection episodes. The rate of bacterial, viral, or protozoal infections was not higher in patients with one or more rejection episodes than in those without.

The temporal relationship between rejection and infection is shown in figure 2. The attack rates

of infection during the 30 days before rejection were compared with those observed during the 30 days following rejection. A total of 17 bacterial, 28 viral, and five fungal infectious episodes were diagnosed in this 60-day interval. The overall attack rate of infections was 44.4 episodes per 1000 patient-days within the 30 days before rejection and reached 94.4 episodes/1000 patient-days in the 30 days following rejection treatment by steroid bolus (OR 0.44; 95% CI 0.3–0.64). The attack rate of bacterial infections was 16.7 vs. 30.6 episodes/1000 patient-days (OR 0.54; 95% CI

0.3–0.98) during the 30-day period before and after rejection treatment respectively. The attack rate of viral infections markedly increased from 19.4 episodes/1000 patient-days before rejection to 58.3 episodes/1000 patient-days after rejection treatment (OR 0.31; 95% CI 0.18–0.53). As shown in figure 2, there were 21 episodes of viral infection (herpes 10; CMV 9; EBV 1; and recurrent HCV 1) in the 30-day period following the steroid bolus compared with seven episodes diagnosed during the 30 days before rejection.

Discussion

In this study, 80% of patients developed an infection post-transplantation. Almost half of these were bacterial with an infection rate that peaked during the first month following transplant. The incidence of fungal infection was higher among patients who developed a graft rejection than among those who did not. The temporal relationship between graft rejection and the occurrence of infection shows that the incidence of both viral and bacterial infection is increased by immunosuppressive supplementation.

The timing of the occurrence of infection, with a peak during the first 4 weeks post-transplantation, has already been described [1–5, 15]. The association between the increased immunosuppressive therapy required to treat rejection and the higher infection rate has also been observed [2, 11, 16].

Our study found that when an arbitrarily defined but clinically relevant period of 30 days before and after the beginning of rejection treatment was surveyed (figure 2), the incidence of viral and bacterial infection increased dramatically after steroid-treated rejection. Notably, 14 of 28 viral infectious episodes were mild (*Herpes labialis*) and treated with topical acyclovir (Zovirax®). Ten episodes of CMV infection occurred and all were successfully treated. The remaining four infectious episodes included two EBV and recurrent hepatitis.

Twenty-four percent of patients developed CMV disease, but only one patient died during CMV therapy with death secondary to bacterial septic shock. The relatively mild complication rate with CMV infection differs from some studies [2, 5] but not from others [1, 7, 17, 18]. We hypothesise that the discrepancy between these findings may be related either to the improvement in viral isolation techniques, diagnosis and treatment of CMV infections, or to the immunosuppressive regimen.

The infection rate in our transplanted patients is similar to that observed in some other studies [3–5, 19], but higher than in those using selective bowel decontamination [20, 21]. There may be various reasons for this discrepancy. First, we did

not start enteral decontamination before surgery and anticipated a delay of 2–4 days before the optimal efficacy of this therapy was attained. This hypothesis is supported by Badger et al. [22], who observed the presence of endotoxaemia in selective digestive decontamination (SDD) patients up to 9 days after the beginning of therapy. Second, if the patient survived, a follow-up period of at least 6 months (by which time SDD should no longer be effective) was required before including a patient in our study. Finally, we used a different antimicrobial regimen to decontaminate the gut from that described in other studies [20, 21]. However, our 1-year and/or global mortality is similar to the majority of recently published series. The SDD effect may then significantly decrease the morbidity associated with infection after transplantation without affecting the mortality rate [23]. Our group reported similar conclusions when SDD was administered to mechanically ventilated patients [24]. In this patient population we found a decreased incidence of nosocomial pneumonia but no effect on mortality. The use of antimicrobial prophylaxis in the clinical setting raises concerns about bacterial and fungal resistance. We failed to identify any patient colonised with vancomycin-resistant enterococci among those hospitalised in our institution during the study period. It is important, however, that these organisms are not endemic in our institution and have been identified in a very low number of cases (data not shown). Nevertheless, oral vancomycin is currently no longer used as prophylaxis at our institution and the oral SDD regimen now administered contains only polymyxin B and neomycin. Furthermore, current immunosuppressive practice now consists of Cellcept® (Roche Inc, Nutley, NJ), FK506 (Merck, Sharp and Dohme, Rahway, NJ) or Neoral® (Novartis, East Hanover, NJ), and Simulect® (Novartis, East Hanover, NJ).

The incidence of fungal infection in the present study was low and comparable with other centres [25] with the abdominal cavity reported as the most frequently infected site. *Candida albicans* was the leading fungal pathogen isolated (84%), and candidaemia was observed in five cases.

Persistent HCV confirmed that the majority of our patients with preoperative hepatitis C end-stage liverdisease had recurrent infection [26]. However, only 18% of the patients had histologically-proven active hepatitis without the accelerated hepatic destruction pattern reported for HBV infection [27]. During the 12 months post-transplantation, in an attempt to prevent or slow down the recurrence of HBV, fresh frozen plasma containing a high titre of hepatitis B antibody was administered. This therapeutic policy resulted in a 37% recurrence rate of hepatitis B, a lower incidence than has previously been reported [28].

Immunosuppression has changed considerably since the present study was started. Nowadays, immunosuppression in liver transplant patients is usually based on tacrolimus given in combination with low doses of corticosteroids. This study was performed over a long period of time but, in consequence, allowed us to have a follow-up period of up to 64 months.

In conclusion, the present study confirms that infection is a frequent and major cause of morbidity and mortality after liver transplantation. Infections occurred more frequently during the first month following transplantation. The abdomen, lung, and bloodstream were the most common sites of infection. Following liver transplantation, rejection is associated with a higher incidence of infection and increased immunosuppressive therapy aggravates the risk of infection.

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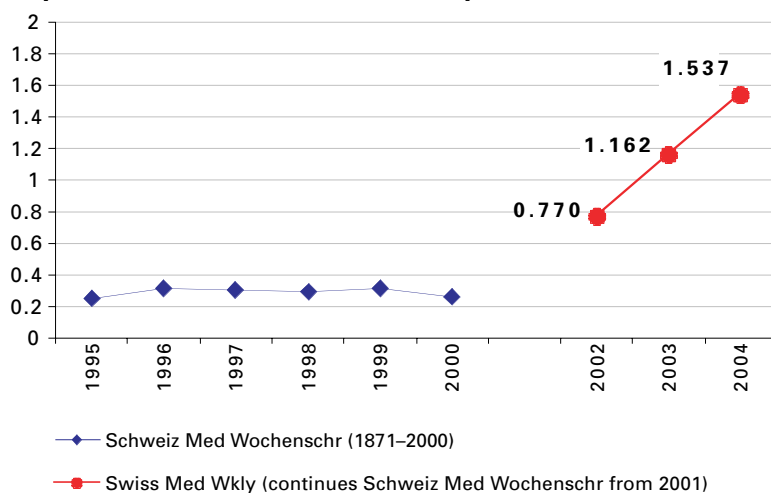
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