Cytomegalovirus Disease as a Risk Factor for Graft Loss and Death After Orthotopic Liver Transplantation

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To determine whether cytomegalovirus (CMV) disease is an independent risk factor for graft loss and death after orthotopic liver transplantation, we performed a 3-year follow-up study of 143 consecutive liver transplant recipients and six patients who underwent retransplantation. Thirty-seven patients (25%) had had CMV disease and were alive after treatment. Fifty-two deaths and eight graft losses occurred. The cumulative incidence of graft failure at 1 and 3 years of follow-up were 40% and 63%, respectively, for patients with CMV disease, compared with 22% and 33%, respectively, for those without CMV disease ($P < .05$, logrank test). Cumulative probabilities of survival for patients with and without CMV disease were 64% and 82%, respectively, at 1 year and 46% and 69%, respectively, after 3 years ($P < .05$, logrank test). Multivariate analysis with use of a time-dependent Cox model showed that previous CMV disease was an independent risk factor for graft loss at 1 and 3 years of follow-up ($P = .04$ and $P = .007$) and for patient survival ($P = .04$ and $P = .01$). Our results indicate that CMV disease is a significant independent risk factor for graft loss and patient survival after liver transplantation.

Orthotopic liver transplantation (OLT) has become the treatment of choice for selected patients with advanced liver disease. The improved success of this procedure has been attributed to refinements in surgical technique, new immunosuppressive protocols, and improved postoperative management, including the control of infectious complications [1]. Cytomegalovirus (CMV) is one of the most important opportunistic pathogens in liver transplant recipients. It is a direct cause of morbidity and mortality and can indirectly influence immunosuppression, making a patient prone to life-threatening superinfection by other opportunistic microorganisms such as *Aspergillus* species or *Pneumocystis carinii* [2–8]. There is evidence that CMV infection can lead to chronic allograft dysfunction [9–13], and CMV infection has been associated with more-severe histological progression of chronic hepatitis in liver recipients with posttransplantation hepatitis C virus infection [14–15]. There are few data in the literature regarding the influence of these indirect effects on graft loss and patient survival [16]. The purpose of the present study was to determine if CMV disease may be a risk factor associated with increased rates of graft loss and death after OLT. The causes of death and graft loss are described.

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Patients and Methods

Patients. Between October 1988 and December 1994, we performed 172 OLTs in 156 patients with end-stage liver disease at Hospital General Vall d'Hebron (Barcelona). The patients were followed up for a maximum period of 3 years after transplantation. All CMV disease episodes except those in which the patient died of CMV disease were considered in the analysis. Thirteen patients (23 grafts) who survived <1 month were excluded from the analysis. Transplantations were performed as described previously [17]. Patients received perioperative prophylaxis with ampicillin and cefotaxime for 72 hours. Beginning in June 1991 (patient 41), prophylaxis with oral co-trimoxazole (160/800 mg/d) was given during the first year. The baseline immunosuppressive regimen consisted of cyclosporin A and a tapering course of corticosteroids. From August 1993 to March 1994, the patients participated in a multicenter, prospective, randomized trial comparing FK506 and cyclosporin A as induction therapy. Rejections were documented by biopsy and treated with 500 mg of intravenous methylprednisolone for 3 consecutive days. Recycled oral corticosteroids were used in cases in which an initial response was followed by sluggish improvement. Refractory rejection was treated for 10–14 days with OKT3 (Orthoclone; Ortho Biotech, Raritan, NJ).

Prevention, diagnosis, and management of CMV infection. The serological status of the donors and recipients was determined with use of ELISA for IgG antibodies to CMV. Initially, no prophylactic measures were taken. Starting in November 1992, ganciclovir (Roche S. A., Madrid, Spain) was administered to the CMV-seronegative recipients and to the patients receiving OKT3. From June 1991 to November 1993, 37 patients received acyclovir (Glaxo S. A., Madrid) as part of a

randomized study of prophylaxis for CMV disease. The occurrence of CMV infection was monitored weekly by performing viral blood cultures (shell-vial cultures and the conventional tube culture technique) until the third month after OLT and thereafter at follow-up visits. When clinically indicated, blood, other body fluids, and tissue specimens were processed for CMV detection. In cases of suspected organ involvement, tissue biopsy specimens were obtained and examined by standard histological (detection of CMV inclusion bodies) and immunohistochemistry techniques. Intravenous ganciclovir (5 mg/kg every 12 hours for 14 days) was administered when CMV disease was documented.

Definitions. The diagnosis of CMV infection was based on isolation of the virus from any body fluid or tissue or on detection of virus in tissue specimens by shell vial assay or tube cell culture. CMV disease included CMV syndrome and CMV focal diseases such as hepatitis, pneumonitis, or gastrointestinal disease. Focal disease was defined as the isolation of CMV from any tissue or body fluid plus compatible histological findings. CMV syndrome was defined as the presence of positive blood cultures for CMV and an illness having two or more of the features known to be related to infection with CMV, including unexplained fever that lasted for $\geq$3 days, associated with one of the following findings: leukopenia ($<$4,000 WBCs/mm^3) or thrombocytopenia ($<$100,000 platelets/mm^3), either of which was present on $\geq$3 consecutive days after the withdrawal of therapy with azathioprine or ganciclovir, or atypical lymphocytosis ($>$5% of peripheral WBCs).

Data analysis. A total of 61 potential risk factors were analyzed. Pretransplantation, intratransplantation, and posttransplantation variables were analyzed for their association with death and graft loss at 1 and 3 years after OLT. Continuous variables were defined as dichotomous variables. The cutoff points were chosen before data analysis and represented an estimate that would be clinically and physiologically relevant. Univariate analysis was done by calculating actuarial survival rates with use of the Kaplan-Meier survival methodology. Statistical comparisons were carried out by using the method of Mantel-Cox (logrank test). Only variables that showed a statistical association with the 1-year or 3-year mortality or graft loss rates on univariate analysis were included as candidate variables for forward stepwise selection in the multivariate time-dependent Cox model analysis. Univariate and multivariate analyses were performed with SPSS (SPSS, Inc., Chicago) version 6.0 for Windows. Differences were considered to be significant at P values of $<$.05.

Results

We studied 143 patients who underwent OLT and six patients who underwent retransplantation. The mean duration of follow-up was 774 days (range, 31–1,095 days). The median age of the 95 men and 48 women studied was 54 years (range, 16–66 years). The most common indication for transplantation was cirrhosis due to hepatitis C virus (48.2% of patients), followed by alcoholic cirrhosis (43.3%). Thirty transplant recipients were CMV seropositive but received CMV-negative donor organs (D−/R+), nine were D+/R−, five were D−/R−, and 99 were D+/+. Baseline characteristics of the patients are shown in table 1.

Table 1. Baseline characteristics of 143 liver transplant recipients.

Variable	Patients with CMV disease	Patients without CMV disease
Median age in y (range)	54 (33–65)	54 (16–66)
No. of males/no. of females	26/11	69/37
Indication for OLT*		
Cirrhosis of indicated etiology		
Hepatitis C virus	16 (43.2)	53 (50)
Hepatitis B virus	3 (8.1)	8 (7.5)
Alcoholism	20 (54)	42 (39.6)
Other	4 (10.8)	6 (5.6)
Malignancies	3 (8.1)	20 (18.8)
Other	6 (16.2)	21 (19.8)
Child score		
A	3 (8.1)	14 (13.2)
B	14 (37.8)	53 (50)
C	20 (54)	39 (36.7)
Donor/recipient CMV serostatus		
−/−	0	5 (4.7)
+/−	5 (13.5)	4 (3.7)
−/+	6 (16.2)	24 (22.6)
+/+	26 (70.2)	73 (68.8)
Median length of transplant operation in min (range)	455 (330–720)	435 (210–800)
Median length of graft ischemia in min (range)	480 (260–910)	472.5 (195–960)
Median U of operative blood transfused (range)	32 (5–115)	22.5 (1–202)
Acyclovir prophylaxis	6 (16.2)	30 (28.3)
Ganciclovir prophylaxis	3 (8.1)	7 (6.6)
Positive crossmatch	2 (5.4)	8 (7.4)
Use of OKT3	12 (32.4)	21 (19.8)
Use of azathioprine	11 (29.7)	28 (26.4)
Median no. of steroid boluses 12 mo after OLT (range)	2 (0–10)	2 (0–23)
No. receiving cyclosporine/FK506	36/1	83/23
Acute rejection	12 (32.4)	41 (38.6)
Recurrent rejection	6 (16.2)	19 (17.9)
Steroid-resistant acute rejection	10 (27)	8 (7.4)
Chronic rejection	6 (16.2)	10 (9.4)

NOTE. Data are number (%) of patients unless otherwise indicated. CMV = cytomegalovirus; OLT = orthotopic liver transplantation; − = seronegative; + = seropositive.

* Fifty-nine patients had more than one liver disease.

CMV disease occurred in 46 (32.2%) of the 143 patients. Twenty-six patients had CMV hepatitis, six had CMV syndrome, seven had pneumonia, one had gastrointestinal CMV disease, and six had disseminated CMV disease. Eleven cases (23.9%) were diagnosed during the first month after OLT, and 38 (82.6%) occurred during the first 6 months after OLT. In

Table 2. Causes of death or retransplantation among orthotopic liver transplant recipients.

Variable	No. (%) of patients
Cause of death (n = 52)	
Infectious causes	
Bacterial pneumonia	12 (23.0)
Sepsis	8 (15.4)
Pneumocystis carinii infection	4 (7.7)
Aspergillus species infection	8 (15.4)
Candida species infection	2 (3.8)
Other	4 (7.7)
Noninfectious causes	14 (26.9)
Malignancy	4 (7.7)
Hemorrhage	3 (5.8)
Stroke	2 (3.8)
Other	5 (9.6)
Cause of retransplantation (n = 8)	
Chronic rejection	4 (50)
Ischemia	3 (37.5)
Relapse of hepatitis B virus infection	1 (12.5)

eight of the 46 cases, CMV disease, including hepatitis (one patient), pneumonia (one), and disseminated CMV disease (six), was found at necropsy. One additional case occurred 2 days before death. Only one of these nine patients (a patient with disseminated CMV disease) died of CMV disease. These nine CMV disease episodes were not included in the analysis of risk factors for death.

Ninety-one of the 143 patients studied were alive at the end of follow-up. Sixty of 149 grafts included in the graft survival analysis had been lost at the end of follow-up. Two cases of graft loss occurred after the recruitment period, and the patients, who underwent retransplantation, were not included in the analysis. The causes of the 52 deaths and the eight graft losses are shown in table 2. The most common cause of death after 3 years of follow-up was an infectious disease (70% of cases). Bacterial infection (either sepsis or pneumonia) was the leading cause and accounted for 20 (38.4%) of the 52 deaths. Disseminated fungal infection occurred in 10 patients; *Aspergillus* species were the most frequent etiologic agents. Fourteen (26.9%) of 52 deaths were due to noninfectious causes. Eight grafts were lost as a result of problems related to chronic rejection or vascular complications that culminated in liver failure.

The cumulative percentages of graft survival at 1 year and 3 years of follow-up were 73.1% and 59.3%, respectively. The significant risk factors for graft loss, as determined by univariate analysis at 1 and 3 years of follow-up, are shown in table 3. Crude univariate analysis of the cumulative graft survival rates at 1 and 3 years after OLT showed that CMV disease was a significant risk factor for graft loss. The cumulative incidence of graft failure in the first year was 40.5% among patients with CMV disease, as compared with 22.5% among those without CMV disease. Differences were more marked after 3 years of follow-up. At that time, the cumulative rate of graft loss was 63.3% among patients with previous CMV disease, compared with 32.8% among those without CMV disease ($P < .05$, logrank test).

The cumulative percentages of patient survival at 1 and 3 years of follow-up were 76.9% and 63.0%, respectively. The significant risk factors for death, as determined by univariate analysis at 1 and 3 years of follow-up, are shown in table 4. The cumulative probabilities of survival for patients with and without CMV disease were 63.8% and 82.2%, respectively, at 1 year of follow-up and 45.9% and 68.9%, respectively, after 3 years of follow-up ($P < .05$, logrank test).

Results of multivariate time-dependent Cox model analysis with use of the variables that were significantly associated on univariate analysis confirmed the importance of previous CMV disease as an independent risk factor for graft loss at 1 and 3 years of follow-up ($P = .04$ and $P = .007$, respectively) and for death ($P = .04$ and $P = .01$, respectively). The analysis disclosed that acute rejection (for graft loss and death at 1 and 3 years of follow-up), positive crossmatch (for survival after 3 years of follow-up), and chronic rejection (for graft loss after

Table 3. Univariate time-dependent analysis (Kaplan-Meier method) of predictors of 1- and 3-year graft survival for 149 recipients of orthotopic liver transplants.

	No. (%) of patients with graft loss		No. (%) of patients without graft loss		P value	
Variable	1 y	3 y	1 y	3 y	1 y	3 y
CMV disease	15 (40.5)	24 (40)	24 (21.4)	14 (15.7)	.04	.002
Acute rejection	21 (53.8)	33 (55)	27 (24.5)	30 (33.7)	.0004	.003
Child score (A-B)	18 (46.1)	29 (48.3)	70 (63.6)	59 (66.2)	.04	.02
Use of azathiprine	20 (51.2)	26 (43.3)	29 (26.3)	23 (25.8)	.004	.01
Use of OKT3	. . .	23 (38.3)	. . .	12 (13.4)	. . .	.0001
Number of blood products	. . .	47 (78.3)	. . .	49 (81.6)	. . .	.004
Chronic rejection	. . .	14 (23.3)	. . .	5 (5.6)	. . .	.0003

NOTE. CMV = cytomegalovirus.

Table 4. Univariate time-dependent analysis (Kaplan-Meier method) of predictors of 1- and 3-year survival for 143 patients with orthotopic liver transplants.

	No. (%) of patients who died		No. (%) of patients who survived		*P* value	
Variable	1 y	3 y	1 y	3 y	1 y	3 y
CMV disease	13 (40.6)	20 (38.4)	23 (20.7)	17 (18.6)	.04	.01
Acute rejection	17 (53.1)	29 (55.7)	29 (26.1)	34 (37.3)	.001	.01
Use of OKT3	. . .	18 (34.6)	. . .	15 (16.4)	. . .	.008
Number of blood products	. . .	39 (75)	. . .	52 (57.1)	. . .	.03
Chronic rejection	. . .	10 (19.2)	. . .	6 (6.5)	. . .	.02
Positive crossmatch	. . .	7 (13.4)	. . .	3 (3.2)	. . .	.02

NOTE. CMV = cytomegalovirus.

3 years of follow-up) were also independent risk factors (table 5).

Discussion

OLT has undergone tremendous development over the past 10 years and is now considered to be routine treatment for end-stage liver disease. It is therefore relevant to determine the prognosis for patients who have undergone OLT and to understand the factors that are related to mortality, and it is particularly important to identify risk factors for graft loss or death that may be modified to improve outcome.

Technical problems and acute rejection have become less important as risk factors for death among orthotopic liver transplant recipients, and infection and chronic rejection have become increasing problems for these patients [18, 19]. The risk factors for graft loss or death that have been reported to date include pretransplantation encephalopathy and prolonged partial thromboplastin time [20], urgency of liver transplantation [21], HLA compatibility [22, 23], use of FK506 in patients with chronic hepatitis C infection who undergo OLT [24], liver diseases of the recipients (e.g., chronic hepatitis B and primary hepatic malignancy) [25, 26], the pretransplantation serum creatinine level [27], and ABO blood group compatibility [28]. The impact of CMV infection on survival was not evaluated in these studies.

CMV is the single most important infectious agent affecting liver transplant recipients, and there is evidence of CMV infection in at least two-thirds of these individuals [2]. During the last few years, substantial progress has been made in the management of CMV infection, but CMV infection remains a major source of morbidity after OLT despite the many advances in early diagnosis and treatment. It has been reported that CMV infection may predispose to other opportunistic infections, especially those due to *P. carinii, Aspergillus fumigatus, Candida albicans,* and gram-negative bacilli, in patients undergoing solid organ transplantation [2–8]. Other indirect effects of CMV infection are related to immunomodulation, i.e., induction of the vanishing bile duct syndrome in liver transplant recipients [9–13] and a more severe histological progression of chronic hepatitis in liver recipients with posttransplantation hepatitis C virus infection [14, 15]. Despite these documented effects, the indirect impact of CMV infection on graft and patient survival has not been extensively studied. Preliminary reports have indicated that CMV infection has no effect on survival [29], but recent data suggest that CMV infection or disease could have an influence on patient and graft survival among liver transplant recipients [30, 31].

Donaldson et al. [30] found that primary and secondary CMV infections were associated with reduced rates of graft survival following liver transplantation only for patients receiv-

Table 5. Multivariate time-dependent Cox model analysis of independent risk factors for graft and patient survival at 1- and 3-year follow-up among orthotopic liver transplant recipients.

	Follow-up at 1 y			Follow-up at 3 y		
Outcome	Risk factor	RR (95% CI)	*P* value	Risk factor	RR (95% CI)	*P* value
Graft survival	CMV disease	1.95 (1.02–3.73)	.04	CMV disease	2.04 (1.2–3.45)	.007
	Acute rejection	2.97 (1.58–5.58)	.0007	Acute rejection	2.08 (1.25–3.48)	.004
				Chronic rejection	2.62 (1.42–4.83)	.002
Patient survival	CMV disease	2.05 (1.01–4.15)	.04	CMV disease	2.05 (1.17–3.62)	.01
	Acute rejection	2.86 (1.43–5.74)	.003	Acute rejection	2.49 (1.11–5.57)	.02
				Positive crossmatch	1.88 (1.08–3.26)	.02

NOTE. CMV = cytomegalovirus.

ing triple immunosuppressive therapy (cyclosporine, prednisolone, and azathioprine). CMV infection was present in 62 (64.6%) of 96 patients with graft loss in the first year after OLT and in 47 (21.3%) of 221 without graft loss ($P < .05$). Van den Berg et al. [31] reviewed the records of 111 adult orthotopic liver transplant recipients. None of the 29 patients without CMV infection died during the first 180 days after OLT, whereas 10 (15%) of 66 patients with CMV infection died during that period ($P < .01$, logrank test). These two studies identified the role of CMV infection as a risk factor associated with death; however, data were obtained only with use of univariate analysis, and the possible effect of CMV infection or other variables should be explored by using multivariate analysis.

Recently, Falagas et al. [16] investigated the effect of CMV disease on 1-year mortality rates among orthotopic liver transplant recipients by using multivariate techniques. These investigators analyzed a cohort of 146 liver transplant recipients and found that the presence of CMV disease was independently associated with higher mortality rates (RR = 3.9, CI = 1.8–8.5, $P = .01$). Retransplantation, the total number of blood-product units administered during transplantation, the presence of invasive fungal disease, and the presence of bacteremia were also identified as risk factors. Falagas et al. maintain that there is a strong association between CMV disease and high mortality rates among orthotopic liver transplant recipients. They recognized that it was difficult to determine whether deaths in their series were directly attributable to CMV disease in patients for whom the causes of death were multifactorial and who were treated before more effective means of preventing or treating CMV disease had been instituted. In addition, it is possible that the CMV disease in their patients was primarily a marker of immunosuppression rather than a direct or indirect cause of death.

Our results are similar to those reported previously. CMV disease was an independent risk factor for reduced rates of graft and patient survival. Our patients with previous CMV disease had a twofold increased risk of death or graft loss after 3 years of follow-up. Other variables were independently significant in the multivariate model, including acute rejection, positive crossmatch (for survival), and chronic rejection (for graft loss).

We tried to identify risk factors with the strongest independent effects on graft loss or mortality. In contrast to Falagas et al. [16], we did not include major bacterial and fungal infections in our model because they are variables directly associated with death and, therefore, more often represent the primary cause of death than possible predictors of mortality. We considered that including the primary causes of death as variables in the model would give erroneous results for identifying risk factors. Moreover, to fully explore the indirect effect of CMV disease on graft and patient survival, patients with active CMV disease at the time of death were not considered in the CMV disease group. This was done to exclude from the analysis deaths directly attributable to CMV. Consequently, we demonstrated that the outcome for patients with a cured episode of CMV disease was poorer, with decreased rates of graft and patient survival at 1 year of follow-up. Furthermore, we found that there were differences in survival after a long period of follow-up (3 years).

It has been reported that CMV disease has different indirect effects in solid organ transplant recipients; these effects are related to CMV-mediated immunosuppression (superinfections by other opportunistic microorganisms) [2–8] and to CMV-mediated activation of the immune system that may end in chronic rejection of grafts [9–13]. As is shown in our study, major bacterial and fungal diseases were the most important cause of death in our population. On the other hand, half of the patients who underwent retransplantation developed chronic rejection. Likewise, in our cohort of liver transplant recipients, CMV disease was a risk factor for invasive fungal disease (multivariate analysis of risk factors in 27 episodes of invasive fungal disease and CMV disease: RR = 4.86; 95% CI = 2.12–11.1; $P = .0002$) and chronic rejection (univariate analysis of risk of developing chronic rejection in relation to CMV disease at 3 years of follow-up: number of episodes of chronic rejection = 18; 29.2% in patients with CMV disease vs. 8.4% in patients with no CMV disease; $P = .02$).

The relation between previous CMV disease and reduced rates of graft and patient survival is of great interest. The mechanism underlying the poorer outcome for CMV-infected graft recipients is still unknown, but this outcome seems to be a consequence of the indirect effects of CMV infection. The increased rate of opportunistic infections and the tendency to develop chronic allograft dysfunction among patients with CMV infection or disease may contribute to the unfavorable outcome for these patients, as compared with those without CMV infection. During the last decade, progress has been made in treating CMV disease, and episodes are usually treated successfully. Our data suggest, however, that treating CMV disease is not enough to avoid its indirect effects or to reduce their impact on mortality.

The question remains as to whether CMV-associated immunomodulation and subsequent superinfection or allograft dysfunction occur following CMV replication or require the presence of CMV disease. In the first case universal prophylaxis would be warranted, whereas in the second case the appropriate strategy would be preemptive therapy. It remains to be established whether the mortality or rate of graft loss associated with CMV disease can be reduced by any prophylactic or preemptive strategies.

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References

1. Bismuth H, Ericzon BG, Roles K, et al. Hepatic transplantation in Europe. Lancet **1987**;2:674–5.
2. Rubin RH. Impact of cytomegalovirus infection in organ transplant recipients. Rev Infect Dis **1990**;12(suppl 7):S754–66.
3. Collins LA, Samore MH, Roberts MS, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. J Infect Dis **1994**;170:644–52.
4. George MJ, Snydman DR, Werner BG, Dougherty N, Griffith J, CMVIG Study Group. Cytomegalovirus disease as a risk factor for fungal disease in orthotopic liver transplant (OLT) recipients [abstract 32]. In: Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy (Anaheim, California). Washington, DC: American Society for Microbiology, **1992**.
5. Paya CV, Wiesner RH, Hermans PE, et al. Risk factors for cytomegalovirus and severe bacterial infections following liver transplantation: a prospective multivariate time-dependant analysis. J Hepatol **1993**;18:185–95.
6. Castaldo P, Stratta RJ, Wood RP, et al. Fungal disease in liver transplant recipients: a multivariate analysis of risk factors. Transplant Proc **1991**;23:1517–9.
7. Tollemar J, Ericzon EB, Barkholt L, Andersson J, Ringden O, Groth CG. Risk factors for deep *Candida* infections in liver transplant recipients. Transplant Proc **1990**;22:1826–7.
8. Kusne S, Torre-Cisneros J, Manez R, et al. Factors associated with invasive aspergillosis and the significance of positive *Aspergillus* culture after liver transplantation. J Infect Dis **1992**;166:1379–83.
9. Paya CV, Wiessner RH, Hermans PE, et al. Lack of association between cytomegalovirus infection, HLA matching and the vanishing bile duct syndrome after liver transplantation. Hepatology **1992**;16:66–70.
10. Bronsther O, Manez R, Kusne S, et al. Posttransplant B, non-A non-B, and cytomegalovirus hepatitis increase the risk of developing chronic rejection after liver transplantation. Transplant Proc **1995**;27:1206–7.
11. Conti F, Dousset B, Archambeau D, et al. Enhanced risk of steroid-resistant acute rejection following pretransplant steroid therapy in liver graft recipients. Transplantation **1995**;60:1104–8.
12. O'Grady JG, Alexander GJM, Sutherland S, et al. Cytomegalovirus infection and donor/recipient HLA antigens: interdependent co-factors in pathogenesis of vanishing bile duct syndrome after liver transplantation. Lancet **1988**;2:302–5.
13. Manez R, White LT, Linden P, et al. The influence of HLA matching on cytomegalovirus hepatitis and chronic rejection after liver transplantation. Transplantation **1993**;55:1067–71.
14. de Otero J, Gavalda J, Vargas V, et al. Does cytomegalovirus (CMV) infection modify the histopathological expression of hepatitis C virus (HCV) infection after liver transplant (LT)? [abstract H75]. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, **1995**.
15. Rosen HR, Corless CL, Chou S, et al. Cytomegalovirus (CMV) infection associated with allograft cirrhosis and failure following liver transplantation for hepatitis C. Hepatology **1995**;24(pt 2):421A.
16. Falagas ME, Snydman DR, Griffith J, et al. Effect of cytomegalovirus infection status on first-year mortality rates among orthotopic liver transplant recipients. Ann Intern Med **1997**;126:275–9.
17. Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation. N Engl J Med **1989**;321:1014–22.
18. Cuervas-Mons V, Martinez AJ, Dekker A, Starzl TE, Van Thiel DH. Adult liver transplantation: an analysis of the early causes of death in 40 consecutive cases. Hepatology **1986**;6:495–501.
19. Backman L, Gibbs J, Levy M, McMillan R, et al. Causes of graft loss after liver transplantation. Transplantation **1993**;55:1078–82.
20. Eckhoff DE, Pirsch JD, D'Alessandro AM, et al. Pretransplant status and patient survival following liver transplantation. Transplantation **1995**;60:920–5.
21. Delmonico FL, Jenkins RL, Freeman R, et al. The high-risk liver allograft recipient. Should allocation policy consider outcome? Arch Surg **1992**;127:579–84.
22. Nikaein A, Backman L, Jennings L, et al. HLA compatibility and liver transplant outcome. Transplantation **1994**;54:786–92.
23. Charco R, Vargas V, Balsells J, et al. Influence of anti-HLA antibodies and positive T-lymphocytotoxic crossmatch on survival and graft rejection in human liver transplantation. J Hepatol **1996**;24:452–9.
24. Casavilla FA, Mateo R, Rakeh J, et al. Impact of hepatitis C virus infection on survival following primary liver transplantation under FK506. Hepatology **1994**;20:133A.
25. Iwatsuki S, Starzl TE, Gordon RD, et al. Experience in 1,000 liver transplants under cyclosporine-steroid therapy: a survival report. Transplant Proc **1988**;20(suppl 1):498–505.
26. Belle SH, Detre KM. Report from the Pitt-UNOS liver transplant registry. Transplant Proc **1993**;25:1137–42.
27. Cuervas-Mons V, Millan I, Starzl TE, Van Thiel DH. Prognostic value of preoperatively obtained clinical and laboratory data in predicting survival following orthotopic liver transplantation. Hepatology **1986**;6:922–7.
28. White DJG, Gore SM, Barroso E, Calne RY. The significance of ABO blood groups in liver transplant patients. Transplant Proc **1987**;19:4571–4.
29. Stratta RJ, Shaeffer MS, Markin RS, et al. Cytomegalovirus infection and disease after liver transplantation. An overview. Dig Dis Sci **1992**;37:673–88.
30. Donaldson PT, Cohen AT, Williams R, Sutherland S. Cytomegalovirus and orthotopic liver allograft survival [abstract P227]. In: Program and abstracts of the 5th International Cytomegalovirus Conference (Stockholm). **1995**.
31. Van den Berg AP, Klompmaker IJ, Haagsma EB, et al. Evidence for an increased rate of bacterial infections in liver transplant patients with cytomegalovirus infection. Clin Transplant **1996**;10:224–31.