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INFECTIONS AFTER LIVER TRANSPLANTATION IN ADULTS: data from a university hospital in southern Brazil (1996-2000)

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ABSTRACT – ***Background*** - Infections after liver transplantations are the most important cause of morbi-mortality. In this study, we assessed the main characteristics of these infections in a southern Brazilian university hospital. ***Methods*** - We conducted a retrospective cohort with 55 patients who underwent orthotopic liver transplantation between 1996 and 2000 in the "Hospital de Clínicas de Porto Alegre", Porto Alegre, RS, Brazil, to characterize the infections that occurred in the group. ***Results*** - One or more infections (average 2.10) were diagnosed in 47 patients, especially during the first month after transplantation. The most common were bacteremia, intra-abdominal infections and pneumonia, predominantly with bacteria, especially *Staphylococcus sp* (and particularly *S. aureus*) and *E. coli*. The mortality rate attributed to infections was high: 17 cases of all deaths (total 27 deaths). Significant risk factors for infections included reoperation, diabetes, biliary stenosis and higher Child-Pugh scores. ***Conclusion*** - Infections remain a severe threat in liver transplant patients, and special efforts should be made to prevent and manage them correctly.

HEADINGS – Liver transplantation. Infection. Risk factors. Immunocompromised host.

INTRODUCTION

Considering solid organ transplants, orthotopic liver transplantation (OLT) is one of those with the highest rates of associated infections[12, 31]. The early studies reported infections in more than 70% of the patients with mortality rates around 80%[7, 19]. The advances in surgical techniques, supportive care units and drugs were significant and infectious related mortality dropped steadly[4, 15, 21].

Serious infections are likely to occur during the first 6 months post-OLT and most of them have bacterial etiology[9, 17, 26]. In this phase, infections are related to the surgical procedure itself, so liver-biliary tract infections are frequent[1, 10, 15], as well as lower respiratory and vascular catheter infections[15, 17]. Other agents as cytomegalovirus (CMV), and herpes virus (HSV) are also prevalent.

Some studies conducted in Brazil had confirmed the importance of infections in our OLT population. TEIXEIRA et al.[33] reported infections rates of 60%, in 90% of them of bacterial etiology. The overall mortality was 31%. A survey performed in São Paulo, SP, Brazil[32] reported rates of 43.2% of nosocomial infections. In our hospital, there are published data only in the pediatric patients[5, 6]. Seventy percent of them had infections in the first month post-transplantation.

METHODS

Fifty-five adult patients who underwent OLT at the "Hospital de Clínicas de Porto Alegre" (HCPA), Porto Alegre, RS, Brazil, between September 1996 and January 2000 were analyzed.

The study was longitudinal (cohort), conducted retrospectively. All patients' records were reviewed, including the entire medical and nurse staff records, the medical prescriptions, laboratory and radiological test results. As a routine at the HCPA, cultures of the organ preservation solution (where the donated liver was kept) were performed. The transplantation protocol included preoperative serological tests for viruses (CMV, HCV, HBV, EBV, HSV, and HIV), Chagas' disease and toxoplasmosis serology in the donor and recipient, and at least a week after the transplant in the latter. Other cultures, microbiologic and serological tests were performed in cases of suspected infection.

We used the criteria of the Center of Disease Control of the United States (CDC) for nosocomial infections[8]. Infections not considered in the CDC criteria, such as cholangitis, were

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defined according to criteria used by KUSNE et al.[15]. For all fungal infections it was required positive culture or biopsy.

The statistical analysis of potential risk factors was performed by Chi-square test for proportions (for cells with n≤5 the Fisher exact test was used) and Cox proportional hazard regression. Risk factors were considered significant with a *P*-value <0.05.

RESULTS

The demographic data are shown in Table 1.

All the patients received steroids, which were started on the day of the surgery and 80% of them had also received cyclosporine. The initial dose of cyclosporine was 10 mg/kg/day, the serum value was monitorized and used to adjust the doses, during the first week after the transplantation the serum level targeted was 400 ng/mL, after this, until the end of the first month post-transplantation this target was 300 ng/mL. For acute and chronic immunosuppression azathioprine was initially used in all cases, while tacrolimus and mycophenolate mofetil were used in a few patients in chronic immunosuppression. For acute rejection, antythymocite globulin and OKT3 were used in three cases.

Antibiotic prophylaxis consisted of cefoxitin and vancomycin, during 48 hours, starting during surgery (this regimen was established by the Committee of Infections Control of the HCPA based on bacterial spectrum coverage). Only two patients had a different prophylactic regimen, because of previous hypersensitivity to the antibiotics. After the transplantation antifungal prophylaxis was maintained for 1 year with oral fluconazole in all cases.

There were no retransplantation cases in our series. One patient also underwent kidney transplantation a few months after liver transplantation.

The follow-up period varied between 1-1,708 days (mean 614.7 days – survival curve in Figure 1). The most frequent infections observed were bacteremia, abdominal infections (mostly cholangitis, followed by intra-abdominal abscesses) and pneumonia (Figure 2).

TABLE 1. Demographics of the adult patients submitted to liver transplantation

Patients (n)	55
Gender/female (n)	22
Age (years)	
Mean (± SD)	45.6± 10.4
Range	18-66
Diabetes (n)*	4
Child-Pugh score (n)	
A+B	19
C	30
Non-cirrhotic patients	6
Indication for transplantation (n)	
HCV Cirrhosis	21
HCV and alcoholic cirrhosis	11
Alcoholic cirrhosis	7
Sclerosing cholangitis	3
Biliary cirrhosis	2
Caroli disease	2
Miscellaneous	9

*Diabetes-defined before transplantation
SD = standard deviation

In our series, 47 of the transplanted patients developed other infections, with an average of 2.1 each. Table 2 demonstrates the first infection presented by the patients studied.

Overall, 27 out of 55 patients died, 17 exclusively from infection. Another six patients died of non-infectious causes, while in four the cause of death was not determined. Twenty of the deaths occurred during the first 30 days after transplantation, while the latest death occurred 458 days after transplantation.

Bacteremia was mostly frequently caused by *E. coli* and *Enterococcus* sp (Table 3). There were only three episodes of fungemia. Two of these patients died.

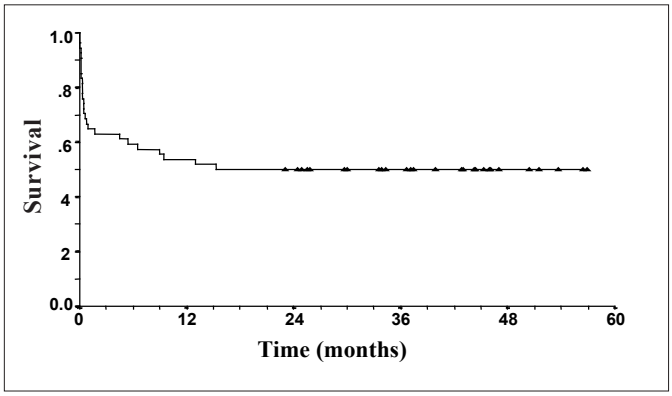

FIGURE 1. Survival curve in adult liver transplanted patients (Kaplan-Meyer)

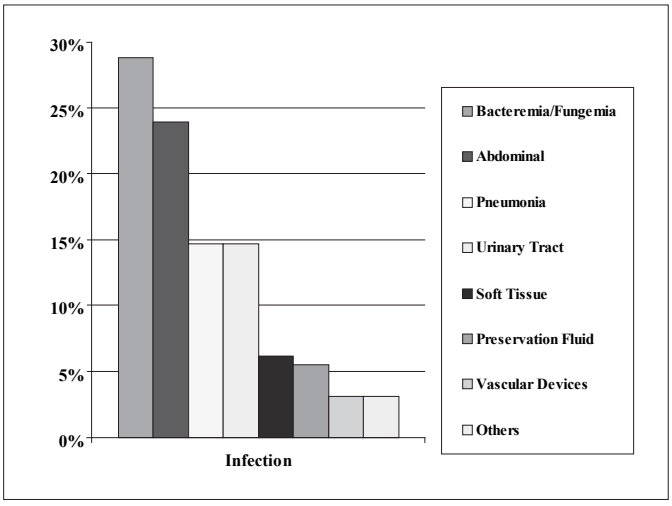

FIGURE 2. Total of non-mucocutaneous infections in adult liver transplanted patients

TABLE 2. The first infection presented by the adult liver transplanted patients

Infections	n	%
Pneumonia	14	29,9
Sepsis	12	25,5
Abdominal infection+cholangitis	11	23,4
Urinary tract infection	5	10,6
Central line infection	3	6,3
Others (eg. skin infection)	2	4,3
Total	47	100

TABLE 3. Microorganisms obtained from blood cultures in adult liver transplanted patients

Microorganism	n.	%
Gram-negative bacteria	28	47.5
E.coli	13	22.0
Klebsiella sp.	4	6.8
Acinetobacter sp.	3	5.1
P.aeruginosa	2	3.4
Enterobacter.sp	2	3.4
B.cepacia	1	1.7
S.maltophilia	1	1.7
C.freundii	1	1.7
F.oryzihabitans	1	1.7
Gram-positive bacteria	28	47.5
***Enterococcus* sp**	8	13.6
S.aureus	7	11.8
S.coagulase neg.	7	11.8
Streptococcus viridans	3	5.1
Streptococcus bovis	2	3.4
Corineiform bacilii	2	3.4
Fungal	3	5.1
Candida sp	3	5.1

TABLE 4. Univariate and multivariate analysis: infections (density of infections) in adult liver transplanted patients according to: reoperation, biliary stenosis, diabetes, Child-Pugh scores and RBPC transfusions

	Univariate			Multivariate		
	n	RR	95% CI	n	HR	95% CI
Reoperation						
yes	20			16		
		4.96*	2.77-8.99		2.19*	1.04-4.73
no	34			29		
Biliary stenosis						
yes	13			10		
		2.69*	1.42-5.18		0.76	034-1.73
no	41			35		
Diabetes #						
Yes	4			4		
		18.76*	6.73-52.26		2.91*	1.09-7.56
No	51			41		
Child-Pugh						
A+B	18			16		
		2.05*	1.10-3.82		1.96	0.93-3.31
C	31			29		
RPBC						
>5	31			28		
		0.84	0.47-1.50		1.32	0.73-2.38
≤5	24			17		

RR = relative risk HR = hazard ratio 95% CI = 95% confidence interval
RBPC = red blood packed cells
*significant, # Diabetes-defined before transplantation
Univariate = Chi-square for proportions (Fisher exact test if cells counts ≤ 5)
Multivariate = Cox proportional hazard regression

Abdominal infections were mostly caused by gram-negative organisms (27 of the 56 organisms isolated), but *S. aureus* was the most frequent pathogen (11 cases). Pneumonia was caused mostly by bacteria of nosocomial origin: *S. aureus* (MRSA) and *P. aeruginosa* were the two most frequent (seven and six cases, respectively). There were 24 urinary infections, with one patient with a kidney transplant and subsequent urethral stenosis having 9 episodes. The organism found in almost 70% of the episodes of all urinary infections was *E. coli*. Only 10 episodes of soft-tissue infections and 5 episodes of vascular catheter-associated infections were identified.

Five patients presented CMV disease, detected by clinic and serologic manifestations; all of these patients had abnormal liver function and pathological alterations in the hepatic biopsy.

Minor infection complications, such as oral candidiasis, cutaneous fungal infections, cutaneous herpes simplex lesions and parasitosis, were considered apart from all the other infections and occurred respectively in nine (oral candidiasis), six (cutaneous infections), seven (cutaneous herpes simplex) and four (parasitosis) cases.

Five potential risk factors for infections and mortality were analyzed: new surgical procedure, biliary stenosis, pre-OLT diabetes mellitus, Child-Pugh classification and the amount of red packed blood cells transfusions. In Table 4 are demonstrated the relative risks associated with them.

None of the factors analyzed were statistically significant for mortality (either using Chi-square test neither Cox proportional hazard regression).

DISCUSSION

In this study the overall mortality was 49%, most of them caused by infections (62.9% of the deaths).

Our survey confirms the importance of postoperative infection as a cause of morbidity and mortality after liver transplantation. Thus over four-fifths of patients had non-mucocutaneous infections, and almost two-thirds of all deaths were related to them. Like others, we found that the most dangerous period for infections was the first month after transplantation[1, 9], when a "first infection" was most common. Infections have been recognized as a major cause of morbidity and death in liver transplant recipients since the early days of organ transplantation. Despite the advances in immunosuppression and surgical techniques the incidence of infections remain high, with great variation between the different centers (range 10%-80%)[4, 14, 15, 32]. Nevertheless, the mortality rate has fallen, though infections are still one of the most important causes of death[4, 15].

We found that the most frequent types of infection included bacteremia, abdominal infections (especially cholangitis) and pneumonias. Almost all previous studies have found the same[4, 10], probably because all patients are submitted to extensive surgical procedures as well as mechanical ventilation and many other invasive procedures such as central vascular lines. Furthermore, these patients also had previous metabolic derangements from their long-term liver disease, were exposed to the nosocomial flora of the ICU, and were given high doses of immunosuppressive drugs during the early post-transplantation period.

The finding that pneumonias were the most common "first infection" probably correlates with mechanical ventilation, and the extensive abdominal surgery, which can cause limitations in ventilation related to pain. Moreover, the patients were ICU during the first days after OLT and it is also one of the most common infections in patients in our ICU[23].

Aerobic gram-negative bacilli were observed in half of all infections in the liver transplanted patients and gram-positive cocci in a similar proportion. In the early stages of transplantation, gram-negative bacterial infections were predominant[26] but during the 1990's gram-positive bacteria emerged as major pathogens[34]. The rise of gram-positive cocci in nosocomial infections seen worldwide in hospitalized patients in the last 10 years (specially *S.aureus* MRSA) as well as the routine prophylaxis with quinolones against spontaneous bacterial peritonitis in cirrhotic patients may have contributed to these trends[3]. Nevertheless, such features are largely influenced by local factors at the center and may vary; thus a 14 years survey at Pittsburgh[30] showed a significant in rise all bacteremias, with a decrease in the proportion of them caused by gram-positive organisms (noteworthy, the percentage of infections by *S.aureus* MRSA raised) but a rise in the proportion caused by gram-negatives, in particular *Klebsiella pneumoniae.*

We had only three cases of fungemia. The rates of severe fungal infections vary in other studies[11, 13, 25, 27], but all agreed that mortality rate is high. Possibly their frequency is diminishing[13, 29], but PATEL et al.[20] also points to the difficulties in diagnosis, which means that this may be underestimated.

Such a consideration also applies to CMV disease, diagnosed in five of our patients. Most other series have reported higher rates with a considerable variation — range 9%-70%[22, 24]. Possibly this is due to difficulties in the diagnosis of CMV infection and also to differences between the definitions of "CMV infection" and "disease related to CMV"[24, 28]. Another possible source of discrepancy is that one of the most frequent presentations of CMV infections in the first 45 days after transplantation is persistent fever, a non-specific feature[8]. In all our patients with diagnosis of CMV infection there was a clear compromise of liver function related to its presence, so all of them had disease related to CMV and not only infection by CMV.

The risk factors that we analyzed included diabetes, biliary stenosis, new surgical procedure, Child-Pugh score and the perioperative use of red blood packed cells. With univariate analysis the first four factors were all significant risk factors, but with multivariate analysis only diabetes and biliary stenosis were. Again, all these risk factors have figured in other studies[2, 9, 10, 26].

Diabetes appeared as the strongest risk factor in our analysis, but this finding may be partly related to few diabetic patients (only four) in our series. Nevertheless, diabetes is known to derange the immunological system, and hence not only predispose to more infections but also increase their severity[16, 18].

Although there has been considerable progress in the control of infections in the liver transplantation patients, they are still a major concern because of the possible severe consequences, including mortality, as we demonstrated in the present study. And this is the paradox in these immunocompromised patients: they are no longer at most risk from their primary illness, but from serious microbial infections.

The described group of patients followed in this study was transplanted during the initial years of our program. During this time, most of them presented with very serious hepatic disease and several co-morbidities. Besides that, were often used organs from marginal donors. Infections in this set were not surprising, and had an important role in the observed outcomes. At this time, patient 1-year survival was as low as 53%. Since them, this rate increased to around 75%.

CONCLUSION

As other studies had demonstrated, we showed that infectious diseases are common after OLT, especially pneumonia and bacteremia caused by gram-negative bacilli, and are frequently related to death. Efforts should be made to prevent and promptly manage these infections by knowing the aspects of local epidemiology and the most important risk factors of this population.

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Souza MV, Barth AL, Álvares-da-Silva MR, Machado ARL. Infecções em pacientes transplantados hepáticos adultos no Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brasil, no período de 1996-2000. Arq Gastroenterol. 2007;44(2):128-32.

RESUMO – ***Racional*** - Infecções são a causa principal de morbimortalidade em pacientes submetidos a transplantes hepáticos. ***Objetivo*** - Avaliar as principais características destas infecções em pacientes de um hospital universitário do sul do Brasil. ***Métodos*** - Uma coorte retrospectiva foi conduzida com os 55 pacientes transplantados hepáticos adultos cuja cirurgia foi realizada entre 1996 e 2000 no Hospital de Clínicas de Porto Alegre, RS, todos aos eventos infecciosos que ocorreram nesta população foram registrados. ***Resultados*** - Uma ou mais infecções (média 2,1 episódios) foram diagnosticadas em 47 pacientes, o período de maior ocorrência destas foi o primeiro mês após a cirurgia. As infecções mais comuns foram: bacteremias, infecções intra-abdominais e pneumonias, a etiologia mais freqüente foi bacteriana, sendo os germes mais comuns os estafilicocos (em particular o *S. aureus*) e a *E. coli.* A taxa de mortalidade associada a infecções foi elevada: 17 óbitos de todos observados na coorte (27 no total). Os fatores de risco para infecção estatisticamente significantes foram: reoperação, diabetes, estenose de via biliar e classificação de Child-Pugh elevada. ***Conclusão*** - As infecções continuam sendo grave ameaça aos pacientes transplantados hepáticos e intenso esforço, que envolve o conhecimento da epidemiologia microbiológica, pesquisa e acompanhamento dos pacientes deve ser empregado, para prevenir e tratar de forma adequada estas complicações.

DESCRITORES – Transplante de fígado. Infecção. Fatores de risco. Hospedeiro imunocomprometido.

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