

# Herpes Zoster After Liver Transplantation: Incidence, Risk Factors, and Complications

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**Herpes zoster is the consequence of the reactivation of latent varicella-zoster infection. Immunosuppression may be a predisposing factor for herpes zoster. We have retrospectively assessed the risk of herpes zoster, the risk factors for its occurrence, and its evolution in a population of 209 consecutive liver transplant recipients. Herpes zoster developed in 25 (12%) of patients. One-, 3-, 5-, and 10-year actuarial rates of herpes zoster were 3%, 10%, 14%, and 18%, respectively. In a case-control study, patients developing herpes zoster were younger, received a higher number of immunosuppressive drugs, and were more frequently receiving mycophenolate mofetil or azathioprine. In multivariate analysis, the only factor related to herpes zoster occurrence was treatment with mycophenolate mofetil or azathioprine. Eight patients (31%) developed postherpetic neuralgia. In conclusion, herpes zoster is a relatively common complication after liver transplantation. It is related to immunosuppressive therapy. Postherpetic neuralgia develops in one third of patients with posttransplant herpes zoster. (*Liver Transpl* 2004;10:1140–1143.)**

Latent varicella-zoster infection is almost universal in adult populations from Europe and North America. Reactivation causes herpes zoster (HZ), which appears as a painful cutaneous eruption with dermatomal distribution. The most frequent complication of HZ is postherpetic neuralgia (PHN), which may persist for months or even years.

The annual incidence of HZ in the general population is 1.5 to 3.0 cases per 1,000 persons.<sup>1</sup> Posttransplant immunosuppression may increase this incidence.<sup>2</sup>

Several studies have evaluated the incidence of HZ after bone marrow transplantation and in patients with human immunodeficiency virus infection, but data on

liver transplant recipients are scarce.<sup>2,3</sup> Therefore, we have performed a retrospective study to investigate the incidence, risk factors, and complications of HZ after liver transplantation.

## Patients and Methods

We have performed a retrospective analysis of our prospectively collected database of all liver transplantations carried out in our center between April 1990 and June 2002. All patients were followed until December 2002. HZ was defined as the appearance of a cutaneous vesicular eruption with a dermatomal distribution. The location, distribution, extension, treatment, and complications of HZ were recorded. PHN was defined as pain in the area of the eruption persisting for more than 30 days after the rash.<sup>4</sup>

Immunosuppressive therapy has been described previously.<sup>5</sup> Calcineurin inhibitors (cyclosporine or tacrolimus), azathioprine, and steroids were administered as primary immunosuppression. Long-term monotherapy based on calcineurin inhibitors was attempted. From 1996, calcineurin inhibitors were partially or completely switched to mycophenolate mofetil (MMF) in the case of renal insufficiency.<sup>6</sup>

Antiviral prophylaxis protocol included the administration of ganciclovir (5 mg/kg/day intravenously for 2 weeks) to patients who were cytomegalovirus negative before transplantation. Those patients with acute rejection who received steroid boluses and/or OKT3 received prophylaxis with oral acyclovir/ganciclovir for 4–8 weeks. Herpes simplex infection was treated with oral acyclovir for one week. Cytomegalovirus disease was treated with ganciclovir (5 mg/kg b.i.d. intravenously for 2 weeks) followed by oral acyclovir for 2 months.

The actuarial incidence of HZ after liver transplantation was obtained by the Kaplan-Meier method. To assess which factors could predispose to HZ, a case-control study was performed. Two controls were obtained for every case, namely patients who had been transplanted immediately before and after the case and were alive at the moment of the diagnosis of HZ. Controls were not matched by age, sex, disease severity, or cytomegalovirus status to make possible the study of these variables as potential risk factors of HZ. The following data were obtained from cases and controls: age; sex; cause of liver transplantation; Child-Turcotte-Pugh status at transplantation; cytomegalovirus serology before transplantation; past history of rejection; antiviral therapy; and immunosuppression (induction immunosuppression with cyclosporine, cyclosporine microemulsion, or tacrolimus; current number of immunosuppressive drugs; current and cumulative doses of

**Abbreviations:** HZ, herpes zoster; PHN, postherpetic neuralgia; MMF, mycophenolate mofetil.

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**Table 1.** General Characteristics of the Patients

	No. of Patients
Age at transplantation (yr)*	55.5 (9.87)
Gender (male / female)	153 / 56
Cause of liver transplantation	
Alcoholic cirrhosis	76
Hepatitis C virus cirrhosis	76
Hepatitis B virus cirrhosis	14
Primary biliary cirrhosis	10
Metabolic cirrhosis	13
Other causes	20
Hepatocellular carcinoma	67
Child-Turcotte-Pugh stage (A / B / C)**	27 / 98 / 78
Acute rejection	54
Calcineurin inhibitor	
Cyclosporine	95
Cyclosporine-Neoral	33
Tacrolimus	81

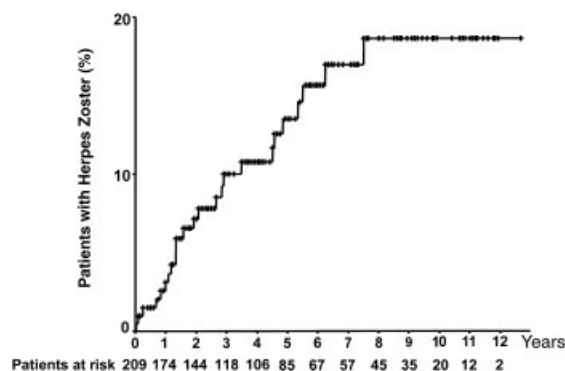
\*Value expressed as mean (SD).  
\*\*Five patients without liver cirrhosis and one patient with fulminant hepatic failure were not included.

prednisone; current use of MMF or azathioprine; and current use of cyclosporine, tacrolimus, or none of them). The possible influence of renal insufficiency (defined as a creatinine level equal or above 1.5 mg/dL) and diabetes mellitus (defined as the need for antidiabetic drugs) were also assessed at the moment of diagnosis of HZ.

To compare both groups, chi-square and Mann-Whitney U tests were used for categorical or continuous variables, respectively. Multivariate analysis (logistic regression) was performed with those variables with  $P < .1$  in univariate analysis.

## Results

General characteristics of the patients are described in Table 1. Twenty-five patients (12%) had HZ. The median time of onset of HZ was 23 months (range, 10 days to 90 months) after transplantation. Actuarial 1-, 3-, 5-, 7-, and 10-year incidences of HZ were 3%, 10%, 14%, 17%, and 18%, respectively (Fig. 1). In 12 of the cases (48%), HZ eruption was located in the thorax. Other locations were neck and shoulder (3 cases), head (3 cases), abdomen (2 cases), and leg (5 cases). All were unilateral. In 5 cases (20%), more than one dermatome was affected. In 4 cases (16%), the eruption recurred after initial healing; two were early recurrences, and the other 2 had HZ recurrence several years after the first eruption. Eight patients (32%) had PHN. In 5 of these patients, PHN resolved within 6 months, but the other 3 patients required pharmacological therapy for more

**Figure 1.** Actuarial incidence of herpes zoster after liver transplantation.

than 2 years. General characteristics of HZ episodes and antiviral therapy are shown in Table 2.

Regarding therapy, 1 patient did not receive antivirals, 4 patients received intravenous acyclovir, 1 patient received intravenous ganciclovir, 5 patients received oral famciclovir, and 14 patients received oral acyclovir. The duration of antiviral therapy was less than or equal to 2 weeks in 19 patients. Four patients received antiviral treatment for 3–8 weeks, and 1 patient was treated for 3 months. There was no relation between the development of PHN and the antiviral drug used or the duration of therapy.

General characteristics of cases and controls are shown in Table 3. Patients with HZ were younger, received a higher number of immunosuppressive drugs, and were more frequently on treatment with azathioprine or MMF. In multivariate logistic regression analysis, the only factor related to HZ was treatment with azathioprine or MMF (hazard ratio, 4.20; 95% confidence interval, 1.48–11.91;  $P = .005$ ).

Five of the 25 patients who had HZ had increases in

**Table 2.** General Characteristics of Herpes Zoster Episodes, Therapy, and Evolution

Extension	Number of Patients
One dermatome	20
More than one dermatome	5
Complications	
Recurrences	4
Postherpetic neuralgia	8
Antiviral therapy (median duration)	
None	1
Acyclovir (intravenous)	4 (1 week)
Acyclovir (oral)	14 (2 weeks)
Ganciclovir (intravenous)	1 (2 weeks)
Famciclovir	5 (one week)

**Table 3.** Characteristics of Cases and Controls

	Cases (N = 25)	Controls (N = 50)	P
Age (yr)*	55.7 (6.24)	57.5 (10.7)	.076
Gender (male / female)	16 / 9	34 / 16	NS
CMV negative	0	3	NS
Indication of transplant			NS
Alcoholic cirrhosis	8	14	
HCV cirrhosis	8	21	
HBV cirrhosis	2	3	
Primary biliary cirrhosis	3	2	
Metabolic cirrhosis	1	3	
Hepatocellular carcinoma	7	20	NS
Child-Turcotte-Pugh (A / B / C)	2 / 11 / 11	11 / 23 / 18	NS
Initial immunosuppression			NS
Cyclosporine	12	26	
Cyclosporine Neoral	6	12	
Tacrolimus	7	12	
Actual immunosuppression			NS
Cyclosporine	16	31	
Tacrolimus	9	18	
Number of immunosuppressive drugs*	2.24 (.18)	1.76 (.12)	.017
AZA or MMF	18	19	.007
Previous rejection	10	18	NS
Antiviral therapy			NS
No	11	27	
Less than 4 weeks	6	11	
More than 4 weeks	7	10	
Diabetes mellitus	3	10	NS
Renal insufficiency	10	12	NS

Abbreviations: NS, not significant; AZA, azathioprine; MMF, mycophenolate mofetil; CMV, cytomegalovirus; HCV, hepatitis C virus; HBV, hepatitis B virus.  
\*Values expressed as mean (SD).

their immunosuppression in the 6 weeks preceding HZ. The causes of these increases were corneal transplantation, retransplantation, treatment of recurrent autoimmune hepatitis, and change of therapy due to nephrotoxicity (association with MMF, and a switch from cyclosporine to tacrolimus). Only one of the 50 controls had an increase in their immunosuppressive therapy in the preceding weeks.

## Discussion

HZ is a consequence of the reactivation of latent infection by varicella-zoster virus. Our paper shows that HZ is not an infrequent complication of liver transplantation. In fact, the incidence of HZ in our series is higher than previously reported.<sup>2,3</sup> This incidence is much higher than the incidence of HZ in the general population,<sup>7,8</sup> and it seems to be comparable to the incidences of HZ found in other solid-organ-transplant recipients<sup>2</sup> and in patients with human immunodeficiency virus

infection<sup>9</sup> but much lower than the incidence occurring after bone marrow transplantation.<sup>10</sup>

As previously observed, the use of antiviral prophylaxis does not seem to prevent the development of HZ after organ transplantation.<sup>2</sup> This finding is not surprising, as the onset of HZ following LT is relatively high, and antiviral prophylaxis is administered in the first few weeks after transplantation. In the same way, a past history of rejection was not related to the development of HZ, as most episodes of rejection happen in the early posttransplant period. HZ seems to be more related to maintenance immunosuppression, because it happened a median of 2 years after transplantation. In this setting, an increase of immunosuppression may trigger the reactivation of HZ. In our series, 20% of HZ happened after recent increases of immunosuppression.

Development of HZ in liver transplant recipients is related to immunosuppressive therapy. In their paper, Gaurishankar et al. found that HZ was 4 times more

frequent in patients receiving MMF than in patients receiving azathioprine.<sup>2</sup> In our series, therapy with azathioprine or MMF was the only factor independently related to the occurrence of HZ.

Despite an older age is a predisposing factor for HZ in the general population, in our series cases were not older than controls. In the posttransplant setting, the weight of immunosuppression as a predisposing factor for HZ may mask the potential effect of age. Furthermore, as younger patients have a higher risk of rejection<sup>11</sup> they usually require a more powerful immunosuppression. In our series, most patients received antiviral therapy with oral acyclovir or famciclovir. This therapy was effective, but 2 patients had early recurrence of HZ, shortly after primary healing. One of them did well with another 1-week course of oral acyclovir. The other received antiviral therapy for 3 months.

One of the most feared complications of HZ is PHN. In this series, one third of the patients had this complication, and for some of the patients with PHN, pain persisted for years. This proportion is relatively high, but it is comparable to the proportion of PHN in immunocompetent patients older than 60 years.<sup>4</sup> Fortunately, none of the patients in this series had any other more severe complication of HZ, such as retinitis, visceral involvement, or other neurological complications.<sup>12</sup>

In conclusion, HZ is a frequent complication after liver transplantation. Its evolution is usually satisfactory with oral therapy, but PHN is a frequent complication. Patients receiving more intensive immunosuppression have a greater risk of developing HZ.

## References

1. Gnann JW, Whitley RJ. Herpes zoster. *N Engl J Med* 2002;347:340–346.
2. Gourishankar S, McDermid JC, Jhangri GS, Preiksaitis JK. Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era. *Am J Transplant* 2004;4:108–115.
3. Gnann JW. Other herpesviruses: Herpes simplex virus, varicella-zoster virus, human herpes types 6, 7, and 8. In: *Transplant Infections*, 1st edition. Philadelphia, PA: Lippincott-Raven; 1998:265–286.
4. Kost RG, Strauss SE. Postherpetic neuralgia: Pathogenesis, treatment and prevention. *N Engl J Med* 1996;335:32–42.
5. Herrero JI, Lucena JF, Quiroga J, Sangro B, Pardo F, Rotellar F, et al. Liver transplant recipients older than 60 years have lower survival and higher incidence of malignancy. *Am J Transplant* 2003;3:1407–1412.
6. Herrero JI, Quiroga J, Sangro B, Giralda M, Gomez-Manero N, Pardo F, et al. Conversion of liver transplant recipients on cyclosporine with renal impairment to mycophenolate mofetil. *Liver Transpl Surg* 1999;5:414–420.
7. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med* 1005;155:1605–1609.
8. Ragozzino MW, Melton LJ III, Kurland LT, Chu CP, Perry HO. Population-based study of herpes-zoster and its sequelae. *Medicine (Baltimore)* 1982;61:310–316.
9. Buchbinder SP, Katz MH, Hessol NA, Liu JY, O'Malley PM, Underwood R, Holmber SD. Herpes zoster and human immunodeficiency virus infection. *J Infect Dis* 1992;166:1153–1156.
10. Gomez-Manero N, Herrero JI, Quiroga J, Sangro B, Pardo F, Cienfuegos JA, Prieto J. Prognostic model for early acute rejection after liver transplantation. *Liver Transpl* 2001;7:246–254.
11. Gildea DH, Kleinschmidt-DeMaster BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med* 2000;342:635–645.