


AUTHOR QUERY FORM

	Journal: JHEPAT Article Number: 3799	Please e-mail or fax your responses and any corrections to: E-mail: proofcorrections.esil@elsevier.sps.co.in Fax: +353-61-709279
---	---	---

Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list. To ensure fast publication of your paper please return your corrections within 48 hours.

For correction or revision of any artwork, please consult <http://www.elsevier.com/artworkinstructions>.

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof. Click on the 'Q' link to go to the location in the proof.

Location in article	Query / Remark: click on the Q link to go Please insert your reply or correction at the corresponding line in the proof
Q1	Please check the edit(s) made in the sentence "Overall...5years", and correct if necessary.

Thank you for your assistance.

Demographics and outcomes of severe herpes simplex virus hepatitis: A registry-based study

Bogdan Moldovan¹, Gilles Mentha¹, Pietro Majno¹, Thierry Berney¹, Isabelle Morard², Emile Giostra², Barbara E. Wildhaber³, Christian Van Delden³, Philippe Morel¹, Christian Toso^{1,*}

¹Transplantation Division, Department of Surgery, Geneva, Switzerland; ²Division of Gastroenterology and Hepatology, Geneva, Switzerland; ³Paediatric Surgery Division, Department of Paediatric, Geneva, Switzerland

Background & Aims: Herpes simplex virus hepatitis is a rare, but severe disease, thus far only documented by case reports and short series. The present study was based on the SRTR registry, and included all listed patients for liver transplantation from 1985 to 2009 with a diagnosis of HSV hepatitis.

Methods: We assessed demographics and outcome of all listed patients, and further conducted a case-control study, matching each transplanted patient with 10 controls. Matching criteria included: transplant status, MELD score ± 5 , transplant date ± 6 months, and age at transplant ± 5 years. During the study period, 30 patients were listed for HSV hepatitis. Of the 30 listed patients, seven recovered spontaneously and five died, prior to transplantation. The remaining 10 children and eight adults were transplanted.

Results: The chance of recovery was significantly higher in children than in adults (7/19 vs. 0/11, $p = 0.02$). In children, survival was similar between HSV patients and the matched controls (5-year survival: 69% vs. 64%, $p = 0.89$). Conversely, survival was poor in adult HSV (5-year survival: 38% vs. 65%, $p = 0.006$), with 62% of them dying within the first 12 months. All three reported post-transplant deaths in children were independent from HSV. Among the seven adult post-transplant deaths, four were related to infection (bacterial, fungal, or viral).

Conclusions: Children listed for HSV hepatitis have a significantly better survival than adults both prior and after liver transplantation. While HSV fulminant hepatitis is an appropriate indication for liver transplantation in children, it should only be performed in selected adult patients in otherwise good condition. © 2011 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Fulminant herpes simplex virus (HSV) hepatitis is a rare condition that can be caused by both HSV types 1 and 2 [1]. It appears most often in very young immunocompetent children or in adults with impaired immunity, including pregnancy, malignancy, HIV-infection/AIDS, and the exposure to immunosuppressive drugs [2,3]. HSV dissemination and hepatitis may be favoured by a large inoculum at the time of the initial infection, the activation of a latent virus, possibly associated with reinfection by a second strain and/or by the presence of a hepatotropic subtype of the virus [4–6]. Signs and symptoms of HSV hepatitis include fever, abdominal pain, nausea, and vomiting. Approximately 60% of patients demonstrate associated HSV-related mucocutaneous lesions [2].

The management of HSV hepatitis includes the use of systemic antiviral therapy, based on acyclovir, and, if required, liver transplantation [6]. Overall outcome is known to be poor, with a high risk of death. Yet, the treatment strategies, while following logical, physio-pathological principles, have so far only been based on case reports or short series. In addition, the limited number of cases did not allow the design of differential management strategies between children and adults.

The present large registry-based study looked at the natural behaviour of HSV hepatitis in patients registered on the transplant waiting list, as well as at the outcome after liver transplantation. Demographics and results were compared between children and adults.

Patients and methods

This study was based on data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States of America (US), submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [7]. The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

The study included patients registered on the liver waiting list for HSV hepatitis from December 1985 to January 2009. These patients were identified based on required, manually entered, pre- or post-transplant diagnosis information, including “herpes” and/or “HSV”. No transplant candidate or transplant recipient was excluded.

Keywords: Herpes; Virus; Liver; Transplantation; Adult; Paediatric; Survival; Outcome.

Received 11 May 2010; received in revised form 21 February 2011; accepted 23 February 2011

* Corresponding author. Address: Department of Surgery, Rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland. Tel.: +41 22 3727693; fax: +41 22 3727707.

E-mail address: christian.toso@hcuge.ch (C. Toso).

Abbreviations: SRTR, Scientific Registry of Transplant Recipients; HSV, herpes simplex virus; MELD, Model for End-Stage Liver Disease; HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; US, United States of America; OPTN, Organ Procurement and Transplantation Network; HRSA, Health Resources and Services Administration; UNOS, United Network for Organ Sharing.



ELSEVIER

4 August 2011

Research Article

Demographics and natural behaviour of patients on the waiting list were compared between children (≤ 18 years at listing) and adults (>18 years at listing). Spontaneous recovery was defined as survival >1 month, in the absence of transplantation.

Post-transplant outcomes were studied following a **case-control** design. Each transplanted patient was matched to **10** controls, based on transplant status (according to UNOS classification), Model for End-Stage Liver Disease (MELD) score ± 5 , transplant date ± 6 months, and age at transplant ± 5 years. The occurrence and date of death were obtained from data reported to the SRTR by the transplant centres and were completed by data from the US Social Security Administration and from the OPTN. Intent-to-treat survival was defined as survival from the time of listing with or without transplantation.

Statistical analyses were performed utilizing Student-*t* and **Mann-Whitney** tests for continuous variables, and Chi-square and Fisher tests for binomial variables. Survivals were assessed using **Kaplan-Meier** curves and compared with log-rank tests. Results were provided as mean \pm standard deviation. Standard alpha level of 0.05 indicated statistical significance. Analyses were conducted using SPSS 17.0 (SPSS, Chicago, IL).

Results

Among the 175,354 patients listed for liver transplantation during the study period, 30 were reported as having HSV hepatitis (17/100,000 listed patients, Fig. 1). Most patients were listed after 1993, with a peak around the year 2000 (Fig. 2A). On average, 1.25 patients were listed each year.

Listed patients were predominantly female (18/12, Table 1). Mean age was 15 ± 19 years, with a biphasic age distribution, including a majority of young children less than 18 months of age and the remaining ones between 14 and 58 years (Fig. 2B). Of note, most of the paediatric patients were very young, with 11 patients listed during the first 2 weeks of life, and four between 1 and 5 months. Most of the patients were acutely sick, on ventilator (60%), listed for an emergency transplantation (87%), and with a MELD score of 27 ± 4 .

Children and adults had significantly differing demographics and outcomes on the waiting list. The male/female ratio tended to be higher in children than in adults ($p = 0.06$). Children demonstrated less advanced liver failure with lower MELD/PELD score, serum bilirubin, and serum creatinine, and higher serum albumin compared to adult listed patients (Table 1). Outcomes on the waiting list were better in children with 7/19 (37%) surviving without transplant, while none of the adults did ($p = 0.02$, Table 1).

Overall, liver transplantation was performed in 18/30 listed patients (60%), including 10 children (56%) and eight adults (44%, Table 1). Mean age of the transplanted patients was 18 ± 20 years; 10 were females and eight males. Most of the transplants were performed in an emergency setting (15/18, 83%).

Post-transplant outcome was assessed in a **case-control** study, and comparing 18 patients with HSV hepatitis to 180 matched controls. As per protocol, both groups had similar transplant UNOS status, MELD score, transplant date, and age at transplantation (Table 2). Overall patient survival after liver transplantation for HSV hepatitis was 60% and 53% at 1 and 5 years, respectively. The outcome was significantly different between children and adults (Fig. 3). Children with HSV hepatitis had a similar post-transplant survival as matched controls (69% vs. 64% at 5 years, $p = 0.89$). Conversely, adult patients with HSV hepatitis had significantly lower survivals than matched controls (38% vs. 65% at 5 years, $p = 0.006$). Of note, 5/8 adult HSV patients (62%) died within the first year post-transplant. None of the deaths observed in HSV children was related to infectious

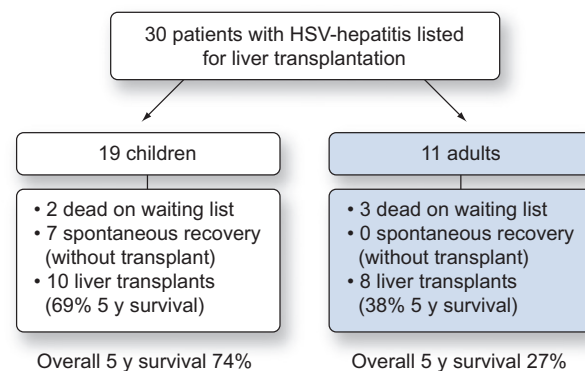


Fig. 1. Flow diagram of patients with HSV hepatitis listed for liver transplantation.

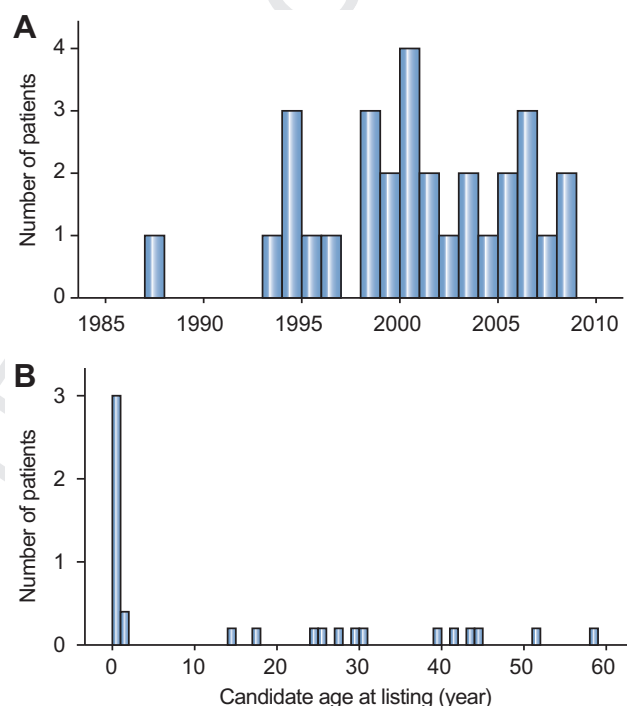


Fig. 2. Histogram showing the distribution of patients with HSV hepatitis listed for liver transplantation, according to the year of listing (A) and the age at listing (B).

diseases, while most of the adults transplanted for HSV hepatitis died of infection-related problems (Table 3).

Intention-to-treat survival from the time of listing, i.e. including non-transplanted patients, was significantly higher in children than adults with HSV hepatitis (74% vs. 27% at 5 years, $p = 0.001$, Fig. 4).

Discussion

This study demonstrates different behaviours and outcomes between paediatric and adult patients with HSV hepatitis on the liver transplant waiting list. Children have higher rates of

Table 1. Demographics of patients on the waiting list.

	Children	Adults	Total	<i>p</i> *
Number of patients	19	11	30	
Mean age at listing (year ± SD)	5 ± 3	51 ± 4	15 ± 19	≤0.001
Gender (male/female)	9/10	9/2	18/12	0.060
MELD at transplant (± SD)	23 ± 4	35 ± 3	17 ± 11	0.049
Serum creatinine level (μmol/L)	75 ± 44	200 ± 49	113 ± 100	0.024
INR level	2.6 ± 0.5	207 ± 0.7	2.4 ± 1	0.970
Serum bilirubin level (μmol/L)	181 ± 67	239 ± 94	239 ± 256	0.250
Serum albumin level (g/L)	33 ± 2.5	24 ± 2.1	28 ± 7	0.090
Serum sodium level (mmol/L)	140 ± 3	133 ± 2	138 ± 7	0.110
On ventilator (%)	11 (58)	7 (64)	18 (60)	0.750
Status at listing (UNOS)				
status 1	17 (90)	9 (82)	26 (87)	0.680
status 2	1 (5)		1 (3)	
status 3	1 (5)		1 (3)	
unknown		2 (18)	2 (7)	
Survival without transplant (%)	7 (37)	0	7 (23)	0.020
Death on the waiting list (%)	2 (11)	3 (27)	5 (17)	0.240
Transplantation (%)	10 (52)	8 (73)	18 (60)	0.280

None of the candidates were reported to have diabetes.

*Children vs. adults.

spontaneous recovery (37% vs. 0%) and improved survivals (69% vs. 38% 5-year post-transplant patient survival).

Hepatitis is a rare complication of HSV infection. With the inclusion of 30 patients, the present investigation is the largest study available thus far. Overall, only 17/100,000 patients were listed for HSV hepatitis. The provided incidence of the disease on the transplant waiting list should only be viewed as an approximation. Due to the nature of the study, it is possible that cases of HSV hepatitis were underreported. In addition, some patients transplanted for acute liver failure of unknown origin may have had undiagnosed HSV hepatitis. This may have been especially the case during the first years of the present study, when diagnostic tests for HSV were not as reliable as today, probably leading to a lower reported rate before the mid 1990's (Fig. 2B). Of note, an optimal diagnosis should include both serological testing and HSV DNA by PCR [8].

While assessing patients on the transplant waiting list, two groups of individuals appeared at risk of HSV hepatitis, namely very young children (less than 5 months) and adults. It is likely that most of the paediatric cases were linked to a vertical transmission from mother to newborn, as described earlier, even in cases of unrecognised maternal HSV infection [9–12]. The database did not allow the assessment of the co-morbidity profile at the time of listing. However, it is possible that some of the adult patients had some degree of immune impairment, linked to medical conditions, such as pregnancy, HIV/AIDS, and the use of immunosuppression prior to transplant [2,3]. It is also interesting to observe that both genders were equally affected in children, but that nearly exclusively females were put on the waiting list in the adult group. The cause of this observation remains unclear, but one can speculate that this group was skewed towards females because of the risk of HSV infection during pregnancy [3].

Severity of HSV hepatitis, was significantly different, between children and adults, with milder diseases presenting in children

Table 2. Demographics of transplanted patients.

	HSV patients	Matched controls	<i>p</i>
Number of patients transplanted	18	180	0.38
Mean age at transplant (year ± SD)	18 ± 20	15 ± 18	0.61
Number of children (≤18 years, %)	10 (56)	111 (62)	
Number of adults (>18 years, %)	8 (44)	69 (38)	
Gender (female/male)	10/8	92/88	0.72
MELD at transplant (± SD)	28 ± 13	20 ± 13	0.83
Transplant status (UNOS)			
status 1	15	148	0.91
status 2	2	26	
status 3	0	5	
not available	1	1	
Cause of liver disease (%)			
HSV	18 (100)		
Biliary atresia		26 (14)	
Total perenteral nutrition-Associated liver disease		12 (7)	
Cryptogenic		11 (6)	
HCV		9 (5)	
Neonatal hepatitis		8 (4.5)	
Primary sclerosing cholangitis		8 (4.5)	
Alcohol		8 (4.5)	
Autoimmune		7 (4.5)	
Tylenol intoxication		6 (3)	
Primary biliary cirrhosis		6 (3)	
Wilson's disease		6 (3)	
Other		73 (41)	

HCV, hepatitis C virus; HSV, herpes simplex virus.

Research Article

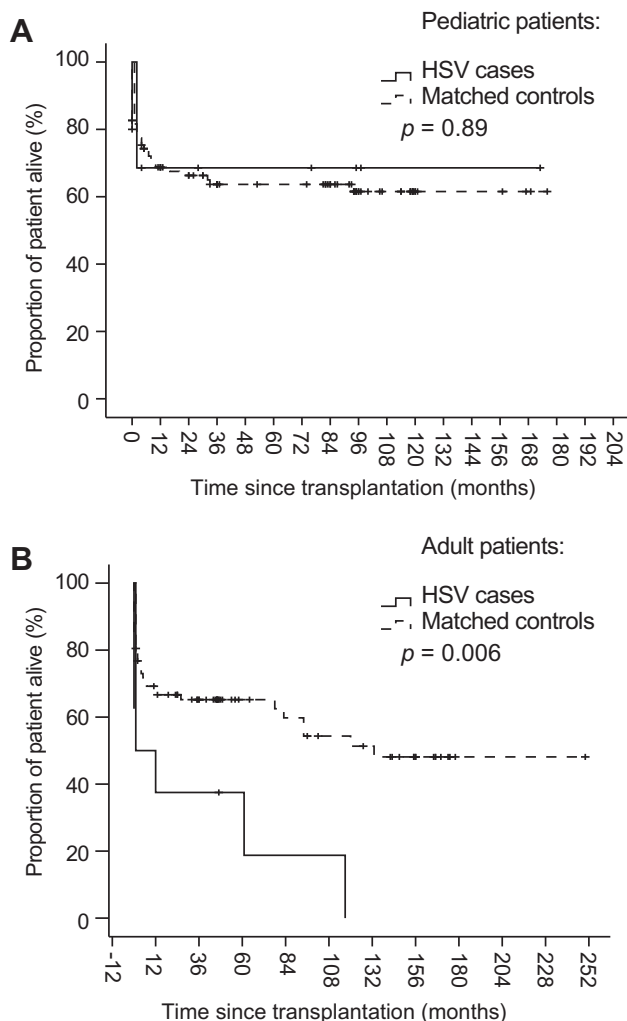


Fig. 3. Post-transplant survival comparing paediatric (A) and adult (B) patients with HSV hepatitis and matched controls. Groups were compared with log-rank tests.

(lower MELD mainly due to creatinine). This observation may be linked to a less severe form of the disease in children and/or to the tendency on transplant services to put children on the emergency transplant list sooner. We would, however, favour the first option, as the rates of spontaneous recovery (37% vs. 0%) and intention-to-treat survival (74% vs. 27% at 5 years) were higher in children than in adults.

Overall, 60% of the listed patients with HSV hepatitis underwent a liver transplantation. Most of them were performed in acutely sick patients and as emergencies. Children had significantly better survivals than adults (69% vs. 38% 5-year post-transplant patient survival), similar to those of matched control children. These post-transplant results further support the hypothesis of a milder form of the disease and/or of the overall better health of children compared with adults with HSV hepatitis. Along the same line, none of the children died of infection, while four adults died of various infectious complications, possibly linked to their poor general condition.

Due to the registry-based nature of the study, several variables could not be assessed, including the type of HSV virus causing the infection (HSV type 1 or HSV type 2). It is, however,

Table 3. Causes of death among transplanted patients.

	HSV patients	Matched controls
Child recipients (%)	3	39
Sepsis (bacterial or fungal)		11 (28.3)
PTLD	1 (33.3)	4 (10.2)
Cardio-vascular disorder	1 (33.3)	5 (12.8)
Multiple organ failure		6 (15.4)
Respiratory failure		4 (10.2)
Primary graft failure		3 (7.7)
Other	1 (33.3)	6 (15.4)
Adult recipients (%)	7	27
Cardio-vascular disorder		4 (14.8)
Sepsis (bacterial or fungal)	3 (43)	10 (37)
Multiple organ failure		3 (11.2)
Viral infection	1 (14)	
ARDS	1 (14)	
Respiratory failure		
Other	2 (29)	10 (37)

PTLD, post-transplant lymphoproliferative disease.

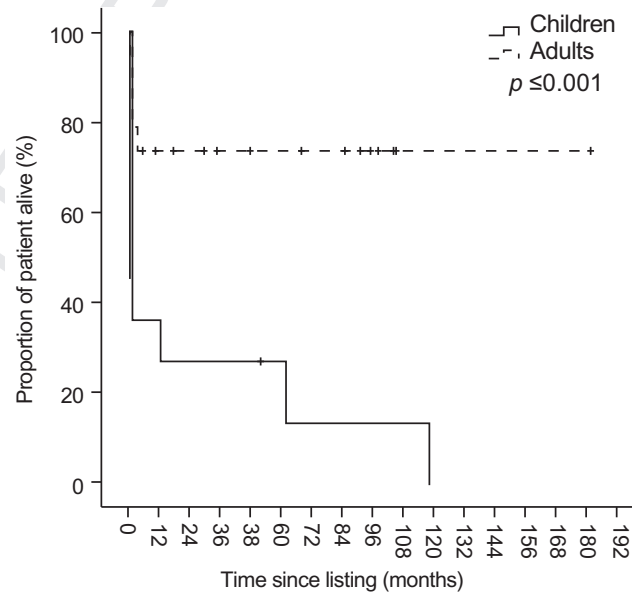


Fig. 4. Intention-to-treat survival from the time of listing for paediatric and adult patients with HSV hepatitis.

known that both agents can lead to the disease, with expected similar outcomes [1]. The use of systemic anti-viral drug, such as acyclovir, could not be assessed, while an early and aggressive treatment has been associated with better outcomes and should be favoured [11,13]. It is also possible that a systematic use of anti-viral therapy can lead to better results than those observed in the present study.

This study shows that HSV hepatitis can affect two categories of patients, young children, probably through a vertical transmission, and adults likely due to an underlying state of immune impairment. In children, higher and acceptable rates of

221 spontaneous recovery and post-transplant survivals have been
222 observed, leading to an overall intent-to-treat survival of 74% at
223 5 years. Conversely, outcome was poor in adults (27% at 5 years
224 from listing), and the indication for liver transplantation in adults
225 should probably be considered only for selected patients in other-
226 wise good general health.

227 **Conflict of interest**

228 The authors who have taken part in this study declared that do
229 not have anything to disclose regarding funding of conflict of
230 interest with respect to this manuscript.

231 **Financial support**

232 C.T. was supported by the Swiss National Science Foundation
233 (SCORE [323230-126233/1](#)).

234 **Special note**

235 The data reported here have been supplied by the Arbor Research
236 Collaborative for Health (Arbor Research) as the contractor for
237 the Scientific Registry of Transplant Recipients (SRTR). The inter-
238 pretation and reporting of these data are the responsibility of the
239 authors and in no way should be seen as an official policy of or
240 interpretation by the SRTR or the [US](#) Government.

References

[1] Pinna AD, Rakela J, Demetris AJ, Fung JJ. Five cases of fulminant hepatitis due to herpes simplex virus in adults. *Dig Dis Sci* 2002;47:750-754. 241-243

[2] Kaufman B, Gandhi SA, Louie E, Rizzi R, Illei P. Herpes simplex virus hepatitis: case report and review. *Clin Infect Dis* 1997;24:334-338. 244-245

[3] Halliday J, Lokan J, Angus PW, Gow P. A case of fulminant hepatic failure in pregnancy. *Hepatology* 2010;51:341-342. 246-247

[4] Miyazaki Y, Akizuki S, Sakaoka H, Yamamoto S, Terao H. Disseminated infection of herpes simplex virus with fulminant hepatitis in a healthy adult. A case report. *Apmis* 1991;99:1001-1007. 248-250

[5] Graham BB, Kaul DR, Saint S, Janssen WJ. Clinical problem-solving. Kiss of death. *N Engl J Med* 2009;360:2564-2568. 251-252

[6] Ichai P, Roque Afonso AM, Sebah M, Gonzalez ME, Codes L, Azoulay D, et al. Herpes simplex virus-associated acute liver failure: a difficult diagnosis with a poor prognosis. *Liver Transpl* 2005;11:1550-1555. 253-255

[7] Scientific Registry of Transplant Recipients. The 2006 SRTR report on the state of transplantation. 5th ed.; 2007. p. 1317-1433. 256-257

[8] Levitsky J, Duddempudi AT, Lakeman FD, Richard J. Detection and diagnosis of herpes simplex virus infection in adults with acute liver failure. *Liver Transpl* 2008;14:1498-1504. 258-259

[9] Stagno S, Whitley RJ. Herpesvirus infections of pregnancy. Part II: Herpes simplex virus and varicella-zoster virus infections. *N Engl J Med* 1985;313:1327-1330. 260-263

[10] Benador N, Mannhardt W, Schranz D, Braegger C, Fanconi S, Hassam S, et al. Three cases of neonatal herpes simplex virus infection presenting as fulminant hepatitis. *Eur J Pediatr* 1990;149:555-559. 264-265

[11] Lee WS, Kelly DA, Tanner MS, Ramani P, de Ville de GJ, McKiernan PJ. Neonatal liver transplantation for fulminant hepatitis caused by herpes simplex virus type 2. *J Pediatr Gastroenterol Nutr* 2002;35:220-223. 266-267

[12] Riediger C, Sauer P, Matevossian E, Muller MW, Buchler P, Friess H. Herpes simplex virus sepsis and acute liver failure. *Clin Transplant* 2009;23:37-41. 268-270

[13] Norvell JP, Blei A, Jovanovic D, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. *Liver Transpl* 2007;13:1428-1434. 271-273

274
275