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Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program

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Introduction: Hepatitis A virus (HAV) infection is a vaccine-preventable disease. The most severe complication in children is fulminant hepatic failure (FHF), estimated to occur in 0.4% of cases; patients with FHF often require a liver transplant (LT). Following another outbreak of HAV infection in Argentina during 2003–2004, a one-dose HAV universal immunization (UI) program was started in 2005, resulting in a reduction in the incidence of HAV infection. We have investigated the impact of HAV UI on the trends in the occurrence of FHF and LT in children.

Methods: All pediatric cases of FHF admitted to four pediatric centers in Buenos Aires during March 1993–July 2005 were retrospectively reviewed, and data of cases during August 2005–December 2008 were collected. Information about demography, HAV infections and vaccination status, diagnostic data for FHF using the Pediatric Acute Liver Failure criteria, clinical laboratory results, encephalopathy, the severity of liver disease using the Pediatric End Stage Liver Disease score, assessment of patients on the LT waiting list using King's College Criteria for LT, treatment given for FHF (pre- and post-transplant), and clinical outcome were collected using a case report form. The frequency and outcomes of HAV-associated FHF and LT cases before and after UI were analyzed.

Results: During the pre-immunization period, March 1993–July 2005, 54.6% (N = 165) of FHF cases were caused by HAV; HAV-associated FHF cases peaked during 2003–2004. During the post-immunization period, August 2005–December 2008, only 27.7% (N = 18) of FHF cases were caused by HAV infection; only one of these patients had received the HAV vaccine (one dose only). The number of HAV-associated FHF cases decreased from 2005, and no cases were reported from November 2006–December 2008. Multivariate analyses showed that the association of FHF with HAV infection rather than other etiologies decreased with increasing age ($P = 0.03$), UI against HAV ($P = 0.002$), and anti-actin antibodies ($P = 0.002$), and increased with increasing weight ($P = 0.0004$).

Conclusions: The number of children with HAV-associated FHF in Argentina has strongly decreased since the initiation of the UI program. Further monitoring is required to confirm the long-term health and economic benefits of UI against HAV infection.

Keywords: hepatitis A vaccine, fulminant hepatic failure, immunization

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Introduction

Hepatitis A virus (HAV) infection is one of the most frequently reported vaccine-preventable diseases worldwide, with an estimated 1.5 million clinical cases occurring each year.[1,2] HAV infection in young children usually causes a mild or asymptomatic

illness, whereas infection in older children and adults more commonly leads to symptomatic disease.[1] The most severe complication of HAV infection is fulminant hepatic failure (FHF), which is characterized by a rapid deterioration in liver function and a high fatality rate.[1] HAV infection has been reported to be the main cause of FHF in more than 58% of cases in children in Argentina.[3,4] It was estimated that FHF occurred in 0.4% of cases of acute hepatitis caused by HAV infection in children aged 1–18 years in Argentina from 1981 to 1996.[5,6] Children with HAV-associated FHF often require a liver transplant (LT), which is associated with high morbidity and mortality, and high costs.[1,2]

In Argentina, the reported overall annual incidence of hepatitis A disease during the period 1995–2004 ranged from 70.5 to 173.8 cases per 100,000 people.[7] A high incidence outbreak of HAV infection occurred during 2003–2004, when the incidence increased from 70.5 cases per 100,000 people in 2002 to 139 and 172.7 cases per 100,000 people in 2003 and 2004, respectively.[7,8] In Buenos Aires, the highest incidence was observed in children aged 5–9 years; 319.7 cases per 100,000 in 2003 and 223.4 cases per 100,000 in 2004.[8] The incidence was also higher in children aged 1–4 years and 10–14 years compared with older children and adults.[8]

A retrospective review of 210 children with FHF (median age 5.33 years; range 1–17.4 years), evaluated in Argentina from 1982 to 2002, found that 61% of cases were caused by HAV infection;[3,8] HAV-associated FHF was reported to account for 20% of LTs in children in Argentina.[5] By comparison, retrospective analysis of 97 pediatric FHF cases (median age 27 months; range 1 day–192 months) treated at the liver unit of a hospital in the UK from 1991 to 2000 showed that only 9.3% of these cases were associated with hepatitis A.[9]

A one-dose hepatitis A vaccine universal immunization (UI) program aimed at children aged 12 months was implemented in Argentina in 2005.[7] There was no catch-up program for 2- to 3-year-old children. In the private market, which represents approximately 12% of the birth cohort, children received two doses of the vaccine at 12–18 months of age. The impact of this immunization policy on the incidence of HAV infection was assessed in a study that analyzed HAV infection rates reported to the National Notifiable Diseases Surveillance System in Argentina (SINAVE) since 1995.[7] Overall vaccine coverage in 2006 was 98% for the single dose (Ministry of Health, Argentina). Disease rates decreased sharply after initiating the vaccination program; the annual incidence of HAV infection for 2007 was 10.2 per 100,000, representing an 88.0% reduction compared with the average incidence for the period 1998–2002 ($P < 0.001$). Reductions were seen in all age groups and all regions in Argentina, even though only children aged 12 months received the hepatitis A vaccine, showing a marked herd-immunity effect.

The objective of this study was to investigate the impact of the inclusion of a hepatitis A vaccine for children aged 12 months in the National Immunization Calendar of Argentina, as indicated by trends in the occurrence of HAV-associated FHF and LT in the pediatric population (<18 years old) in four pediatric transplant centers.

Patients and methods

Study design, population, and treatments

This study involved a retrospective review of all pediatric cases of FHF and LT caused by FHF due to HAV during 1 March 1993–31 July 2005, and the collection of data from all cases of FHF and LT caused by FHF due to HAV during 1 August 2005–31 December 2008. Four pediatric centers in Buenos Aires, Argentina participated in the study; the Hospital Nacional de Pediatría Prof. Dr Juan P Garrahan, the Hospital Universitario Fundación Favaloro, the Hospital Italiano, and the Hospital Austral. Together, these centers treated the most severe FHF cases and undertook >98% of all LT in children in Argentina during the study period. The remaining FHF cases (<2%) were treated at three other LT centers for children in Argentina; these centers handled mainly mild and moderate cases.

All pediatric cases of FHF admitted to one of the four centers from March 1993 to December 2008 were included in the study. Children were aged >3 months to <18 years (the pediatric LT centers included in the study treated patients up to 18 years old) with FHF according to the Mieli-Vergani definition.[10] The following information was collected using a case report form: demographics, HAV infections identified by measuring IgM anti-HAV, HAV vaccination status, diagnostic data for FHF using the Pediatric Acute Liver Failure criteria,[11] hematology and clinical chemistry laboratory results, assessment of encephalopathy, measurement of the severity of liver disease using the Pediatric End Stage Liver Disease score, assessment of patients on the LT waiting list using King's College Criteria for LT, treatment given for FHF (pre- and post-transplant), and clinical outcome (recovery, death in waiting list, and transplantation). Patient data were available only to physicians at participating institutions. Data were recorded in Microsoft Excel (2003; Microsoft, Redmond, WA); in accordance with local regulations, no personal patient data were recorded in the database. The

database could only be accessed by the investigator and authorized personnel at each institution.

Statistical methods

Categorical variables were compared using a chi-square test. For continuous variables, *t*-tests and Kruskal–Wallis tests were used according to the distribution of each variable. Odds ratios and their 95% confidence intervals were reported. Statistical significance was declared with a two-tailed *P* value less than 0.05.

In addition to the analysis of all cases, two further analyses were done. The characteristics and outcomes of patients with HAV-associated and non-HAV FHF were compared, and a univariate analysis was done to identify variables associated with the occurrence of HAV-associated FHF (the reference category was HAV-associated FHF). A multivariate logistic model was then built to test variables independently associated with HAV-associated FHF; variables that had reached a *P* value of ≤0.1 in the univariate analysis (age, weight, UI against HAV, and anti-actin antibodies) were included using a forward stepwise approach. The characteristics and outcomes of patients with HAV-associated FHF during March 1993–July 2005 and August 2005–December 2008 were also compared.

Statistical analyses were performed using SPSS (v 11.5; SPSS Inc, Chicago, IL).

Results

Characteristics and outcomes of FHF cases

During the study period, 367 patients were admitted to one of the four pediatric centers with FHF. The median (interquartile range [IQR]) age of patients was 4 (1–8) years. Patients had severe liver dysfunction, as shown by biochemistry results, and were critically ill; the majority of patients (83.1%) had encephalopathy, and the median grade of encephalopathy was 3. Characteristics and outcomes of patients with FHF are summarized in Table 1. Only 16.3% of patients recovered from FHF without needing LT. On-list mortality was high (21.8%), and patients who received LT had an acute graft rejection rate of 46.5% and a mortality rate of 27.9%.

Causes of FHF cases

The causes of FHF by etiology are shown by year in Figure 1 and during the study overall in Figure 2. Over the study period, almost half of cases (49.9%) were caused by HAV infection; HAV-associated FHF cases peaked in 2004. Other etiologies included cases where the cause was indeterminate, autoimmune disease, Wilson disease, or *Amanita phalloides.* The number of cases of FHF caused by HAV decreased each year after 2004; 18 cases (27.7%) from August 2005–October 2006, and no cases from November 2006–December 2008.

HAV-associated FHF compared with FHF of other etiology

Characteristics and outcomes of patients with HAV-associated FHF compared with FHF of other cause are summarized in Table 1. Patients with FHF caused by HAV were younger compared with patients with non-HAV FHF. The mean (standard deviation) international normalized ratio was 6.71 (2.9) and 5.9 (3.3) in patients with HAV-associated FHF and non-HAV FHF, respectively ($P = 0.03$). Encephalopathy was experienced by 90.2% and 81.5% of patients with HAV-associated FHF and non-HAV FHF, respectively ($P = 0.02$). Acute graft rejection after transplantation was experienced by 38% and 54.8% of patients with HAV-associated FHF and non-HAV FHF, respectively ($P = 0.01$). Mortality was experienced by 25.7% and 38.9% of patients HAV-associated FHF and non-HAV FHF, respectively ($P = 0.04$).

Multivariate analysis showed that the association of FHF with HAV rather than another etiology decreased with increasing age, UI against HAV, and anti-actin antibodies. The association of FHF with HAV rather than another etiology increased with increasing weight. There was no co-linearity between variables. The results of the multivariate analysis are summarized in Table 2.

Impact of the introduction of the anti-HAV vaccine in Argentina

The coverage rate of hepatitis A vaccination in Argentina from 2002–2008 is shown in Figure 3. During the pre-immunization period March 1993–July 2005, before starting the UI, 54.6% (165/302) of FHF cases were caused by HAV. During the post-immunization period August 2005–December 2008, after the introduction of UI against HAV in 2005, only 27.7% (18/65) of FHF cases were caused by HAV infection (see Figure 2). Only one of these patients had received the hepatitis A vaccine; one dose was given when the child was 12 months old and in good health, and FHF was diagnosed when the child was aged 2.3 years.

The characteristics and outcomes of patients with HAV-associated FHF during March 1993–July 2005 and August 2005–December 2008 are summarized in Table 3. During August 2005–December 2008, patients with HAV-associated FHF appeared to be older; the median (IQR) age of patients with HAV-associated FHF during March–August 2005 and

Table 1 Characteristics and outcomes of patients with fulminant hepatic failure, and comparison of patients with fulminant hepatic failure due to hepatitis A virus and fulminant hepatic failure of other etiology

			Comparison of FHF due to HAV with FHF of other etiology		
	HAV	**Non-HAV**	**OR (95% CI)**	***P* value**	**All patients**
Number of cases, n (%)	183 (49.9)	184 (50.1)	–	–	367
Female, n (%)	86 (47)	89 (48.4)	0.94 (0.63–1.43)	0.79	192 (52.3)
Patients included after UI against HAV, n (%)	18 (9.8)	47 (25.5)	0.31 (0.17–0.57)	0.0002	65 (17.7)
Age (years)					
Mean (SD)	4.9 (4.3)	5.9 (2.7)	–	0.02	5.33 (4.2)
Median (IQR)	4 (2–7)	5 (1.5–8)	–	0.083	4 (1–8)
Height (cm), mean (SD)	108.4 (2.3)	114.7 (2.9)	–	0.005	111.34 (2.6)
Weight (kg), mean (SD)	19.6 (12.6)	23.5 (14.1)	–	0.005	21.6 (13.1)
INR, mean (SD)	6.71 (2.9)	5.9 (3.3)	–	0.03	6.31 (3.1)
Prothrombin time (seconds), mean (SD)	17 (11)	17 (12)	–	0.77	17 (12)
Total bilirubin (mg/dL), mean (SD)	23.2 (8.2)	25 (9.1)	–	0.07	24.09 (9.7)
Conjugated bilirubin (mg/dL), mean (SD)	16.2 (7.2)	16.8 (7.1)	–	0.3	16.49 (7.3)
Albumin (g/dL), mean (SD)	2.8 (1.3)	2.9 (1.0)	–	0.15	2.48 (1.1)
Serum creatinine (mg/dL), mean (SD)	0.51 (0.4)	0.49 (0.6)	–	0.55	0.50 (0.4)
Serum sodium (mEq/L), mean (SD)	136.3 (11.7)	136.1 (11.1)	–	0.77	134.1 (12.1)
Anti-actin antibodies, n (%)	3 (1.6)	23 (12.5)	0.11 (0.03–0.39)	0.0002	26 (7.1)
Anti-LKM1 antibodies, n (%)	0 (0)	4 (2.2)	–	0.0002	4 (1.0)
Anti-smooth muscle antibodies, n (%)	25 (13.7)	42 (22.4)	0.49 (0.28–0.86)	0.01	67 (18.3)
Anti-nuclear factor antibodies, n (%)	0 (0)	21 (11.4)	–	0.0002	21 (5.7)
Anti-HCV antibodies, n (%)	0 (0)	2 (1.1)	–	0.07	2 (0.5)
Encephalopathy, n (%)	165 (90.2)	150 (81.5)	2.08 (1.08–4.01)	0.02	305 (83.1)
Grade, median (IQR)	3 (1– 4)	3 (1– 4)	–	0.9	3 (1– 4)
PELD Score (median, IQR)	42 (35–49)	40 (33–48)	–	0.87	42 (35–49)
Outcomes					
Recovery, n (%)	30 (16.4)	30 (16.3)	1.0 (0.57–1.75)	0.98	60 (16.3)
Death in waiting list, n (%)	39 (21.3)	41 (22.4)	0.93 (0.57–1.54)	0.80	80 (21.8)
Transplant, n (%)	113 (61.7)	113 (61.4)	1.0 (0.66–1.54)	0.94	226 (61.6)
Acute graft rejection, n (%)[a]	43 (38)	62 (54.8)	0.51 (0.29–0.89)	0.01	105 (46.5)
Re-transplant, n (%)[1]	17 (15)	13 (11.5)	1.36 (0.59–3.16)	0.55	30 (13.3)
Death, n (%)[1]	29 (25.7)	44 (38.9)	0.54 (0.30–0.99)	0.04	63 (27.9)

Note: [a]A patient may experience one or more of these outcomes after LT.

Abbreviations: HAV, hepatitis A virus; FHF, fulminant hepatic failure; HCV, hepatitis C virus; LKM1, liver kidney microsomal type 1; OR, odds ratio; CI, confidence interval; n, number of cases; UI, universal immunization; SD, standard deviation; IQR, interquartile range; INR, international normalized ratio.

August 2005–December 2008 was 4 (3–8) years and 6 (1–10) years, respectively ($P = 0.023$).

Discussion

Since June 2005, the National Immunization Calendar in Argentina has included one dose of hepatitis A vaccine at 12 months of age. Hepatitis A disease rates decreased sharply after the initiation of the vaccination program. The magnitude of the decline observed make it unlikely that the reductions reflect the cyclic nature of hepatitis A incidence that was observed in the pre-vaccination era.[12] In addition to the introduction of a vaccination program, socioeconomic development, including improved sanitation and health education, also reduces HAV transmission.[1] We are not aware of any major countrywide improvements in sanitation or health education in Argentina during the study period.

Here we report that during March 1993–July 2005, before UI against HAV was introduced, 54.6% of FHF cases were associated with HAV infection. A previous study in Argentina, which retrospectively collected data from 1982–2002, reported that HAV infection was the main cause of FHF in 61% of cases in children aged 1–18 years.[3] HAV infection was estimated to be the cause of FHF in 58% of cases in children in another study in Argentina, which retrospectively reviewed cases from 1992 to 2003.[4] A retrospective analysis in Brazil has reported that 39% of FHF cases in children recorded during a 10-year period were associated with HAV infection.[13] Between 1994 and 2009, acute HAV infection was the cause of 18% of pediatric FHF cases included in a prospective study in Chile.[14] In a prospective, multicenter study that included suspected FHF cases in Latin American countries (Argentina, Brazil, Chile, Colombia, Costa Rica,

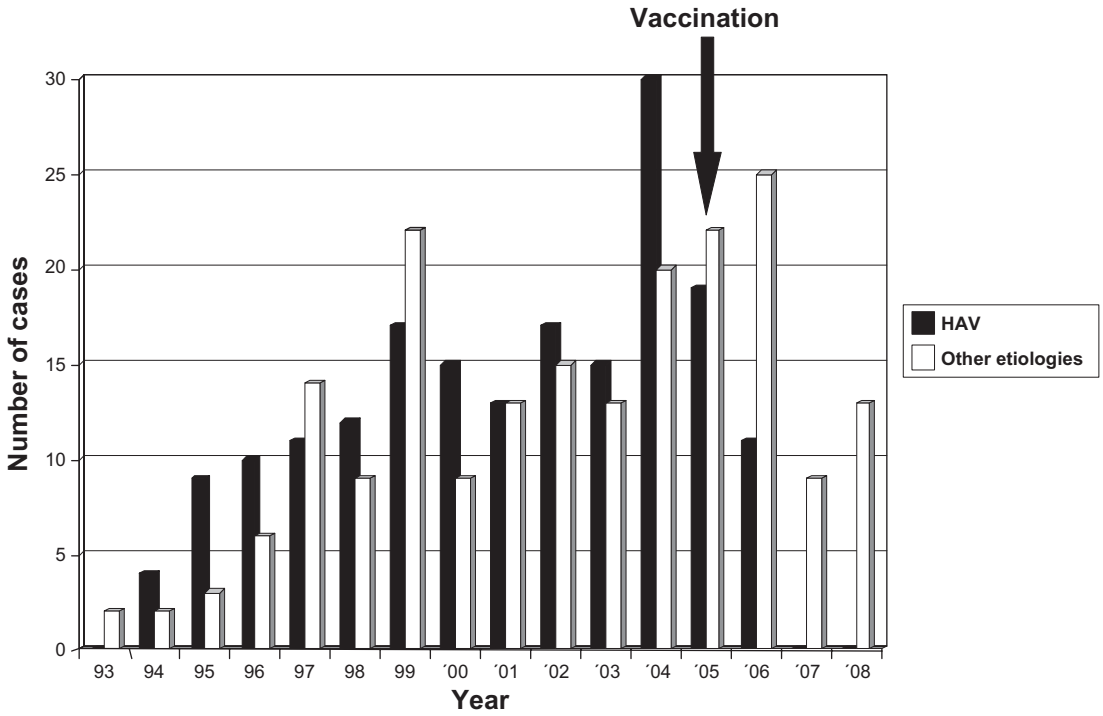

Figure 1 Number of fulminant hepatic failure cases caused by hepatitis A virus (HAV) or other etiologies each year. Other etiologies included cases where the cause was indeterminate, autoimmune disease, Wilson disease, or *Amanita phalloides*. There were similar numbers of cases of indeterminate cause pre- and post-HAV universal immunization.

and Mexico) during 2001–2002, 43% of FHF cases were associated with HAV infection.[15] Therefore, HAV has been a major cause of FHF in children in Argentina and other Latin American countries.

We have investigated the impact of the introduction of UI against HAV on the number of cases of FHF caused by HAV in children treated at the four main LT centers in Argentina; no additional LT centers were created during the study period. We found that the number of cases of HAV-associated FHF has declined since the introduction of UI. During March 1993–July 2005, just over half of FHF cases were associated with HAV infection; the median (IQR) age of these patients was 4 (3–8) years. During August 2005 –December 2008, only 27.7% of FHF was caused by HAV infection; the median (IQR) age of these patients was 6 (1–10) years, and only one of these patients had received the hepatitis A vaccine (one dose only). From November 2006 to December 2008, no cases caused by HAV were recorded. Consistent with this, multivariate analysis to test variables that are independently associated with HAV-associated FHF showed that for subjects with FHF, the probability that the FHF was due to HAV infection rather than other causes decreased with UI against HAV, increasing age, and anti-actin antibodies, and increased with increasing weight.

Israel was the first country to introduce an inactivated hepatitis A vaccine into its National Childhood Immunization program; a two-dose universal hepatitis A immunization

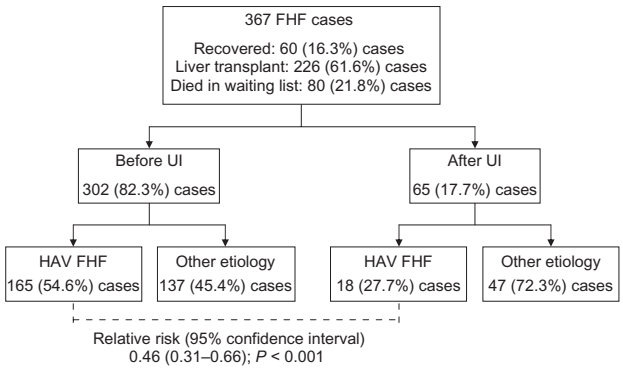

Figure 2 Causes by etiology of cases of fulminant hepatic failure (FHF) during the study.
Abbreviations: UI, universal immunization; HAV, hepatitis A virus.

Table 2 Multivariate analysis of independent variables associated with fulminant hepatic failure due to hepatitis A virus compared with fulminant hepatic failure of other etiology

Variable	OR (95% CI)	*P* value
Age (years)	0.80 (0.66–0.98)	0.03
HAV universal immunization	0.29 (0.13–0.64)	0.002
Weight (kg)	1.11 (1.01–1.19)	0.002
Anti-actin antibodies	0.10 (0.02–0.48)	0.0004

Abbreviations: HAV, hepatitis A virus; OR, odds ratio; CI, confidence interval.

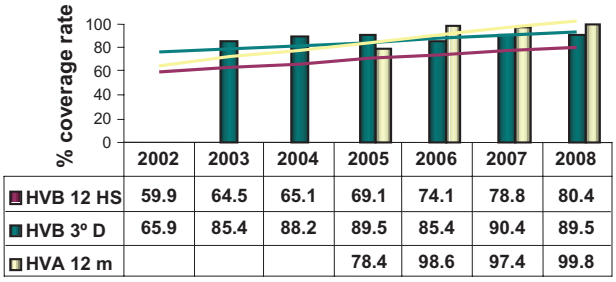

Figure 3 Coverage rate for hepatitis B virus (HVB) and hepatitis A virus (HAV) vaccination in Argentina 2002–2008 (HVB 12 HS - coverage rate of HVB at 12 hours of life; HVB 3° D - coverage rate of third HVB dose; HVA 12 m - coverage rate of HA virus at 12 month of age). Data source: Ministry of Health, Argentina.

program aimed at children aged 18–24 months (without a catch-up campaign) was started in 1999.[16–18] Hepatitis A vaccination coverage in children aged <5 years and 5–14 years immunized with at least one dose of vaccine increased from 9% and 15% in 1998 to 89% and 68% in 2007, respectively.[17] Analysis of data from an ongoing passive national surveillance program showed that there was a sharp decline in HAV disease rates across all age groups within the population after initiation of the vaccination program.[16,17] The annual incidence of hepatitis A infection declined by 95% from 142.4 cases per 100,000 people in 1998 to 7.6 cases per 100,000 people in 2007.[17] Mass hepatitis A vaccination programs have now been introduced in regions of the US, Italy, Spain, and Australia; these programs have led to a rapid decline in HAV disease incidence that has been maintained among vaccine recipients and across other age group.[19–23] However, the effect of hepatitis A vaccination on the incidence of FHF associated with HAV has so far not been determined for any of these vaccination programs.

Spontaneous recovery from FHF without LT was observed for only 16.3% of patients in our study. This recovery rate is low compared with the spontaneous recovery rates of around 30% reported in previous studies

Table 3 Characteristics and outcomes of patients with fulminant hepatic failure due to hepatitis A virus during March 1993–July 2005 and August 2005–December 2008

	March 1993–July 2005	August 2005–December 2008	OR (95% CI)	*P* value
Characteristics				
Number of cases	165	18	–	–
Female, n (%)	75 (45.5)	11 (61.1)	1.88 (0.69–5.10)	0.20
Age (years)				
Mean (SD)	4.9 (3.2)	5.7 (4.1)	–	0.04
Median (IQR)	4 (3–8)	6 (1–10)	–	0.023
Height (cm), mean (SD)	107. 6 (4.6)	115.2 (3.5)	–	0.02
Weight (kg), mean (SD)	19.4 (2.3)	22.4 (4.7)	–	0.02
INR, mean (SD)	6.6 (1.9)	7.4 (2.8)	–	0.03
Prothrombin time (seconds), mean (SD)	17 (6)	16 (6)	–	0.06
Total bilirubin (mg/dL), mean (SD)	23.4 (8.6)	21.5 (8.9)	–	0.05
Conjugated bilirubin (mg/dL), mean (SD)	16.3 (6.9)	15.4 (7.0)	–	0.01
Albumin (g/dL), mean (SD)	2.98 (1.1)	2.7 (1.2)	–	0.28
Serum creatinine (mg/dL), mean (SD)	0.51 (0.4)	0.44 (0.4)	–	0.19
Serum sodium (mEq/L), mean (SD)	136.2 (11.3)	137.3 (10.4)	–	0.16
Anti-actin antibodies, n (%)	3 (1.8)	0 (0)	–	0.05
Anti-LKM1 antibodies, n (%)	0 (0)	0 (0)	–	1.0
Anti-smooth muscle antibodies, n (%)	18 (10.9)	7 (38.7)	0.28 (0.09–0.89)	0.02
Anti-nuclear factor antibodies, n (%)	0 (0)	0 (0)	–	1.0
Anti-HCV antibodies, n (%)	0 (0)	0 (0)	–	1.0
Encephalopathy, n (%)	147 (89.1)	18 (100)	–	0.14
Grade, median (IQR)	3 (1–4)	3 (1–4)	–	0.91
PELD Score (median, IQR)	43 (35–48)	45 (34–49)	–	0.89
Outcomes				
Recovery, n (%)	28 (17)	2 (11.1)	0.61 (0.13–2.81)	0.52
Death in waiting list, n (%)	35 (21.2)	4 (22.2)	1.06 (0.32–3.43)	0.92
Transplant, n (%)	101 (61.7)	12 (66.7)	1.26 (0.45–3.54)	0.65
Acute graft rejection, n (%)[1]	40 (39.6)	3 (16.7)	0.3 (0.07–1.23)	0.1
Re-transplant, n (%)[a]	17 (16.8)	0 (0)	–	0.01
Death, n (%)[a]	28 (27.7)	1 (5.5)	0.18 (0.01–1.38)	0.12

Note: [a]A patient may experience one or more of these outcomes after LT.

Abbreviations: UI, universal immunization; OR, odds ratio; CI, confidence interval; n, number of cases; SD, standard deviation; IQR, interquartile range; INR, international normalized ratio; HCV, hepatitis C virus; LKM1, liver kidney microsomal type 1.

of pediatric patients with FHF.[9,24,25] However, spontaneous recovery rates of 15%–20% have been reported for patients with severe FHF.[26,27] The centers included in our study generally treated the most severe cases of FHF; mild or moderate cases of FHF are treated at peripheral centers, where the spontaneous recovery rate is closer to published data. A retrospective analysis of cases of FHF due to HAV with an indication of LT found that costs of treatment were high, and LT indication in FHF due to HAV delayed LT treatment for other patients with unpreventable conditions.[4]

There are some limitations to our study. The analysis did not include mild and moderate cases of FHF that were treated at three other LT centers for children in Argentina; therefore our results slightly underestimate the number of FHF cases occurring each year. However, these three centers treated <2% of FHF cases, and we do not consider that their inclusion in our analysis would change the observation that the number of cases of HAV-associated FHF has declined since the introduction of UI. Collection of data by chart review may be limited by incomplete documentation (missing charts, missing information), problems in interpreting and verifying information found in the documents, and variance in the quality of information recorded by medical professionals. This study was done during a short period of time after implementation of the UI program, so further monitoring is required to confirm the long term health and economic benefits of UI against HAV infection and to exclude the potential role of natural post-infection immunity owing to the high incidence of infection in previous years in children aged <18 years.

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Disclosure

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